The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference

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Welcome

Good morning. I'm Richard Jackson. I'm from the Centers for Disease Control and Prevention here in Atlanta. I'd like to welcome you all to Atlanta and thank you for joining us for this meeting on the *Health Impact of Chemical Exposures During the Gulf War, A Research Planning Conference*. We're getting a slightly late start, but I just want to thank all of you who have come a great distance to help us grapple with, think about, and figure out where we're going to go with this very difficult, complex issue. Everyone that looks at it has a different insight in how one should deal with and approach this.

We have many distinguished persons on the panel with us today. Most noticeably, Congressman Bernie Sanders, and after I ask my colleagues Ruth Kirschstein and Peter Mazzella to do a welcome, I will introduce the Congressman formally. Ruth.

Ruth Kirschstein, MD
Deputy Director
National Institutes of Health
Bethesda, Maryland

Good morning. I'm Ruth Kirschstein, the Deputy Director of the National Institutes of Health, and I'm really very pleased to greet you and to welcome you on behalf of NIH. The breadth of

participation in this important research planning conference is especially pleasing. We are delighted to see veterans who are joining us with university based research scientists and physicians, representatives from other relevant constituent groups, members of the public, our colleagues from the CDC, the Agency for Toxic Substances and Disease Registry, and other federal agencies.

I am particularly pleased to greet Congressman Bernie Sanders whose interest in the health of Gulf War veterans was the initial driving force for this conference. I first met Congressman Sanders just over a year ago January 15, 1998, and we quickly established common ground in a sharing of a deep concern about our Nation's Gulf War veterans who are suffering form illnesses with symptoms ranging from minor discomfort to severe disability. And I can say to the Congressman, and to all of you, that Dr. Drue Barrett of the CDC and her staff have done an absolutely wonderful job in seeking input from Gulf War veterans during the planning process, and ensuring key involvement of the veterans in the conference itself.

It is our commitment and hope that the conference will be an important step towards identifying appropriate research directions, and I exhort you to listen carefully to one another, to share ideas openly, to participate actively, and to move toward the important goal of moving on, as Congressman Sanders will say, with the research agenda. We cannot afford to do less. And so I welcome you, and I know that we want to acquire all the new knowledge that will help prevent, detect, diagnose, and treat this disease and other disabilities, not only among Gulf War veterans, but indeed, for all of our Nation's citizens. Thank you very much.

Dr. Richard Jackson

Thank you Ruth. Next I'd like to ask Captain Peter Mazzella, the Director of the Office of Military Liaison and Veterans Affairs of the Office of Public Health and Science with the Department of Health and Human Services, to please welcome you.

CAPT Peter Mazzella
Director, Office of Miliary Liaison and Veterans Affairs
Office of Public Health and Science
Department of Health and Human Services
Washington, DC

Thank you. Good Morning. On behalf of the Department of Health and Human Services, I would like to echo the words of Dr. Kirschstein and Dr. Jackson. I am welcoming each of you to this important conference. I would like to thank Congressman Sanders for his efforts in supporting the work that made this conference possible. I would also like to acknowledge the very hard work and dedication of two people who have made the next two and a half days possible, namely Dr. Drue Barrett and Mr. Phil Talboy of the Centers for Disease Control and

Prevention.

We in the Department appreciate the efforts that you have made to get here and to contribute your thoughts, but most of all, we appreciate all the work that you will be doing during the conference to help us get closer to the answering of some of the many questions being asked by our Gulf War veterans.

In developing the agenda, we realized that we were unable to include all scientists who have been active in Gulf War health issues. Thus, in order to include input from persons who are not on the agenda, we have structured the meeting to allow for participation from the audience. Specifically, we have devoted the second session of each workgroup, March 1st from 10:15 to 12 noon, to conference attendees so that they may provide their input to the workgroup members. In addition, we have scheduled a Veterans' Forum for the evening of February the 28th, tonight, to allow veterans in the audience to voice their concerns and provide their input regarding research priorities. If you would like to provide your input during these public input sessions, we request that you place your name on the sign-up lists at the registration table. We all walked past them to get here. This will allow us to estimate the amount of time that will be available to each speaker.

The goal of the conference is to develop research recommendations for future directions. Our research recommendations will be solidly based on the best science available. We at the Department of Health and Human Services wish you good luck in your deliberations, and we look forward to working with you in developing recommendations that will help us achieve our common goal – the improved health and well-being of our Nation's veterans and their families. Thank you.

Dr. Richard Jackson

It is both an honor for the Centers for Disease Control and Prevention, and for me personally, to introduce to you the Honorable Bernard Sanders, Congressman from Vermont. On January 3rd, 1991, Bernard Sanders came to Congress as Vermont's only Representative in the House, and the first Independent elected to Congress in 40 years. Congressman Sanders was sworn in for his 4th term in office in 1997. He serves on the House Banking and Financial Services Committee, and on the Government Reform and Oversight Committee.

Congressman Sanders has a long history of involvement in environmental health and safety issues. He successfully introduced the Cancer Registries Amendment Act which created a nationwide system of cancer registries to provide basic data on environmental causes of cancer. He initiated Congressional hearings which led to the Carpet and Rug Institute developing labels for all carpets alerting consumers that carpeting contains chemicals which can cause illness in consumers who are chemically sensitive. Congressman Sanders co-sponsored the Indoor Air Quality Act of 1993 designed to fund research and abatement strategies to address the growing problem of unhealthy

indoor air. In 1994, Congressman Sanders received the American Academy of Environmental Medicine's Jonathan Foreman award for his contribution to the field of Environmental Medicine. One of Congressman Sanders' main priorities this session has been finding answers to the health concerns of Gulf War veterans.

Before coming to Congress, Mr. Sanders served as Mayor of Burlington for four successive terms. His accomplishments as Mayor included building affordable housing, revitalizing the city's waterfront in downtown, initiating arts, youth, and women's programs, and increasing voter turnout by more than fifty percent. Burlington was recognized as one of the three most livable cities in America, and Congressman Sanders was chosen as one of the 20 best Mayors in the United States by the *U.S. News and World Report.*

Before serving as Mayor, the Congressman worked as a writer, documentary producer, and director of the American People's History Society. Before coming to Congress, he taught at Harvard University and at Hamilton College.

It's a great honor for all of us to have the Congressman here present with us today, and we'd like to thank him for joining us.

The Honorable Bernard Sanders (I-Vermont)
U.S. House of Representatives

Dr. Jackson, thank you very much, and Dr. Kirschstein thank you, and Dr. Mazzella, and I want to thank all of your staffs at the NIEHS and the CDC for putting together what I think will be perhaps the most important conference on the issue of Gulf War illness. And I want to thank very much the researchers and the physicians from all over the country who have joined us today to try to better understand why close to 100,000 men and women who served in the Gulf continue to suffer from a wide variety of ailments.

Before I get into the thrust of my remarks, despite this lovely, kind introduction of Dr. Jackson, I'm really not a very nice guy, and some of what I will say will not be very nice because I think it is terribly important for us not simply to pat each other on the back, and not simply to have a conference in which we exchange ideas, as important as that may be. But I think it is very important, and I'll get into this in a moment, to understand that by and large 8 years after the war, the United States Government has done a rather poor job in responding to the needs of tens of thousands of veterans, that we must stop what has been going on for many years, that we must turn it around, and if all that happens out of this conference is a lovely exchange of ideas, then we have failed. What we must do from this conference is bring together the best minds in the country, radically change where we have gone, develop a sense of urgency so that in the coming months and years, we can finally say to Gulf War veterans, "We now understand what is causing your problems, and we're beginning to effectively treat you."

Now, let me just say a few words as to how I got involved in the issue. That is that, during the last session of Congress, I was on the Human Resources Sub-committee of the House Government Reform Committee which was led by Congressman Chris Shays of Connecticut, who in my sense of things, did a fantastic job. That committee, in my view, perhaps did as much as any committee in the Congress to better understand what was going on. As a member of that committee, over a 19 month period, we held 11 hearings receiving testimony from veterans, from scientists, from physicians, from the Department of Defense, from the VA, from the CIA, from the GAO, and from other government agencies. I think Chris did an extraordinary job trying to bring forth as much information as he possibly could.

Both emotionally and intellectually, I can tell you that those hearings were very trying and difficult. We heard tragic testimony from some veterans who are very, very ill, and I fear may not have much time left on this earth. We heard bureaucratic and arrogant testimony from some government officials who appeared not to have a clue as to what was going on, who appeared not to be paying attention at all to the veterans who were suffering, and who appeared to be, from my perception, living in a totally other world. We heard extremely interesting testimony from scientists and researchers who challenged us with their ideas, and I know some of them are here today, and I want to thank them very much for their efforts on this issue.

Now, what I want to do, the effort of this conference is to exchange ideas, let me quote to you, and I'll do this a little bit from what I believe is one of the more valuable documents that has been produced in recent years, and that is the report that came out of the committee. What Congressman Shays and I agreed was that we just didn't want 11 hearings. We wanted to bring together some recommendations, and some conclusions, and some analyses. And it's published in this report, and we're happy to get it to any person here who would like a copy of it. But let me quote directly from some of that report. Quote:

> After 19 months of investigation and hearings, the sub-committee finds the status of efforts on Gulf War issues by the Department of Veterans Affairs, the Department of Defense, the CIA, and the Food and Drug Administration to be irreparably flawed. We find those efforts hobbled by institutional inertia that mistakes motion for progress. We find those efforts plagued by arrogant incuriosity and a pervasive myopia that sees a lack of evidence as proof. As a result (*and here's the important point*) we find current approaches to research, diagnosis, and treatment unlikely to yield answers to veterans' life or death questions in the foreseeable, or even far distant future. (*I agree with that conclusion*). Further, 6 years and hundreds of millions of dollars have been spend in the effort to determine the causes of the illnesses besetting Gulf War veterans. Yet, when asked what progress has been made healing sick Gulf War veterans, VA and DoD can't say where they've been and concede they may never get where they're supposed to be going. (*Let me continue*). Finally, (*important point*) we reluctantly conclude (*and I pushed for this conclusion*) that responsibility for Gulf War illnesses, especially the

research agenda, must be placed in a more responsive agency independent of the DoD and VA.

Then we also briefly touched on some of the findings in terms of diagnosis. This is what the committee concluded after a lot of work:

1. VA and DoD did not listen to sick Gulf War veterans as to possible causes of their illnesses.

2. The presence of a variety of toxic agents in the Gulf War theater strongly suggests exposures have a role in causing, triggering, or amplifying subsequent service-connected illnesses.

3. Gulf War troops were not trained to protect themselves from the effects of exposure to depleted uranium dust and particles.

4. Pyridostigmine bromide, PB, can have serious side effects and interactions when taken in combination with other drugs, vaccines, chemical exposures, heat and/or physical exercise.

5. VA and DoD health registry diagnosis protocols relied on the unfounded conclusion that there were no chemical, biological, or other toxic exposures to U.S. troops in the Gulf War theater.

6. VA and DoD health registry diagnosis protocols continue to be based on the unwarranted conclusion that unless there is an immediate and acute reaction, exposures to chemical weapons and other toxins do not cause delayed or chronic symptoms.

7. Prematurely ruling out toxic exposures as causative, VA and DoD doctors relied on diagnoses of psychosocial disorder and post traumatic stress disorder to explain Gulf War veterans' illnesses.

8. There is no credible evidence that stress or PTSD causes the illnesses reported by many Gulf War veterans.

9. Accurate diagnosis of veterans' illnesses remains difficult due to inadequate or missing personnel medical records, missing toxic detection logs, and unreleased classified documents.

10. Accurate diagnosis of veteran's illnesses was also hampered by the VA's lack of medical expertise in toxicology and environmental medicine. (*A very important point, indeed*).

11. Exposures to low levels of chemical warfare agents and other toxins can cause delayed chronic health effects.

12. Neither the VA nor the DoD has systematically attempted to determine whether sick Gulf War veterans are any better or any worse today than when they first reported symptoms.

13. Treatment of sick Gulf War veterans by VA and DoD to date have largely focused on stress and PTSD.

Now, those are the types of hearings that I sat through. And those are the conclusions that we reached. But further, as Vermont's sole member to Congress, not only did I attend those meetings, but obviously, I spoke with many of the Gulf War veterans in my own state. I was very lucky to have with me Don Edwards, who was the Adjutant General of the National Guard in the State of Vermont when the war broke out, who sent the men and women overseas, and then Don later joined my staff. So he was able to give me some expertise that was very important. And in discussions with Vermonters, what I discovered is that they are suffering from many of the same problems that veterans all over the country are suffering from – short term memory loss, mental confusion, rashes, headaches, mood swings, gastrointestinal problems – all of the same problems the vets all over the country are suffering from, and the same problems that we heard before our committee.

I will not forget talking with 20 or so, we had different meetings around the state, veterans in Springfield, Vermont, a small town in the Southern part of our state. And I remember speaking to them. I said, "Well, tell me, do any of you suffer from short-term memory loss?" And they all broke out laughing in a kind of sad laugh, and they told, each one went around the room saying, "Yeah, when I get in the car and I go some place, I sometimes can't remember where I'm going." And then they continued to talk, and they told me about walking in a grocery store or the supermarket and they get sick when they come near the odor of detergents. Or the fact that their wives can no longer wear perfume because they get sick around that. Some of these guys are automobile mechanics, and they can't work around automobiles because the solvents make them sick, or fuel exhaust makes them sick. I have to tell you that Vermont is, of course, a small state. Don and I sent out recently . . . and one of the good things that's happened, and I want to be very clear about saying it, that some of you may know that finally, after 8 years, there is now going to be a treatment trial developed by the VA, and I want to congratulate Dr. John Feussner for putting that together. The bad news is that it has taken 8 years. The good news is that it is finally going to happen. It's going to test several important hypotheses. And Don and I were trying to get Vermonters to participate in the trial. We sent out 650 letters to invite people to meetings, and we had over 135 veterans from our own state coming to those meetings, which tells me that maybe the problem is even more severe in terms of number of people who are ill than we had previously believed. I should also say that one of the problems is that a lot of folks who are ill may not be coming forward because they they're still in active duty, they're still in the National

Guard, and they are a little bit nervous about losing their positions.

Let me just say that, in my view, the inactivity and in some cases the duplicity, on the part of the VA and the DoD has significantly increased cynicism among members of the armed forces, veterans, and the general public. There is clearly something very wrong when 8 years after the war, with so many veterans hurting, that there has not yet been one treatment trial until very, very recently.

Now, where do we go from here? I think most importantly, we cannot continue the paradigm which has led us down the path of nowhere. We cannot allow the DoD and the VA to continue to say, as they do, that, "We don't know the cause of the problem. We don't know how to treat Gulf War veterans who are ill. But we damn well do know that anyone out there who has an idea that is different or that might be controversial is wrong."

I remember, and I'll conclude on this remark, that when I spoke to veterans in my own state who are really hurting, and I said to them, "Look, this is a difficult problem and we don't really know the answers of it, but there are different scientists out there who are coming up with different ideas, and if we can give you a treatment that will not make you worse, obviously we don't want to do that, but we're not guaranteeing success, are you prepared to undertake that? Are you prepared to get involved in that treatment trial?" Every hand in the room went up. And I have said to Dr. Feussner and I want to say to all of you right now, you will not be criticized for trying something and then concluding that it doesn't work. You will be criticized and must be criticized for year after year after year telling the people, "We don't know the cause, and we don't have any treatment."

I believe that there are some serious scientists, and researchers, and physicians out there who are coming up with ideas that may not fit the concepts held by some of the folks in the VA and the DoD. But what we have to say is, after 8 years, the VA and the DoD have not done a good job. So, what we have to say is, let's open the doors to new ideas. Let's be prepared. Some of those ideas will be wrong. But we cannot continue to say to our veterans and the people doing serious work out there, "Sorry, we know the answers, and the answer we know is that we don't know anything."

So, I would hope that out of this conference come 2 things:

1. A wonderful sharing of ideas, and I want to congratulate the NIEHS and the CDC for bringing together some of the best minds in the country, thank you very, very much. And they deserve credit, they've done a good job on this conference.

2. But, again, if all that happens is we have an exchange of ideas and 8 years later we come back and say, "We don't know anything, we have no treatment for 100,000 people who

may be ill," then we have failed. And I don't want to fail, and I know that you don't want to fail. So, let us make a pledge that out of this conference comes treatment trials, comes some serious work which finally addresses the problems of our vets.

Thank you very much.

SESSION 1
Background: Gulf War Chemical Exposures and Their Health Impact

Dr. Richard Jackson

Thank you very much Congressman Sanders. You certainly have given this conference a strong, and powerful, and compelling charge. We appreciate that. Thank you.

It's time to turn to our Keynote Address. This is by Dr. Swanson, Professor of Family Practice and Director of the Cancer Center at Michigan State University. Dr. Swanson.

Keynote Address:
The Gulf War Experience: Current Findings and Future Directions

G. Marie Swanson, PhD, MPH
Professor of Family Practice/Director
Cancer Center, Michigan State University
East Lansing, Michigan

Well, Congressman Sanders, you certainly are a challenging person to follow. If the slide projector's on, I'd like to just start. Well, good morning, and I'd like to thank Dr. Drue Barrett, and Dr. Jackson, and the Centers for Disease Control for inviting me to present this *Overview of Persian Gulf Health Concerns and Outcomes*. I want to comment that I recognize that this conference is focused upon the health impacts of chemical exposures, but I have been asked to provide a broad overview of Persian Gulf health research. It won't probably be as exciting as what Congressman Sanders had to say, but I do hope it will provide a database background for you, and some leads for things that can be done now.

Clearly, there are many illnesses and symptoms experienced by Persian Gulf veterans, and many of these occur at higher rates than among veterans not deployed to the Persian Gulf. This is seen, as I will show you, among the United States, United Kingdom, and Canadian veterans. What is more difficult than simply defining these health outcomes is determining why these health effects have occurred.

I'd like to give you a couple of pieces of history here. These data probably look somewhat boring from one perspective, but historically, it's important to know that we have looked at war for centuries. There's an interesting book that I took the first couple of slides from called *War and Public Health*, and I believe it's the first time that public health academically has dealt with many of the health consequences of war.

In the 19th century, doctors first began to count and analyze the nature of battlefield casualties. And early nursing studies provided the first statistical data on mass casualties, the sort of things that you see here. These were rather simple and straightforward. They looked at battle and non-battle deaths in relatively straightforward categories such as those that were killed in action or died of wounds. What's most important about this slide is the disease category was almost entirely infectious diseases, and what we can see, since these are deaths per one thousand soldiers per year of warfare, is that the rate of non-battle deaths from infectious disease has declined radically over time. Changes in weaponry, in military strategy, and in medical services all have modified morbidity and mortality and the nature of those outcomes associated with warfare. As these deaths that we show here from infectious disease have dropped over time, deaths from non-combat accidents have risen. They were 3% of deaths during the Civil War, 16% during World War II, and 45% during the Persian Gulf War.

The next slide simply shows the number of military deaths per year of warfare. These are not rates, so they're not really easy to compare. And, of course, the type of warfare radically changed the causes of death. During the Civil War, 75% of combat deaths were due to bullet wounds and 9% due to explosives. Whereas, during the Korean War, 28% of deaths were due to bullet wounds and 64% due to explosives, so that has changed. In guerilla wars, it's well known that 30% to 40% of deaths are due to land mines. In all of these, improvements in curative, rehabilitative, and preventive medicine over time have dramatically reduced mortality from wounds and from infectious diseases.

This is not the first time that we have been concerned about environment, and environment isn't a straightforward concept. I served in Michigan on the Agent Orange Commission, and of course, there were many environmental concerns there about health effects that were seen after the Vietnam War. Over time, there have been consistent health concerns, and general categories of exposures and risk factors have been looked at. Some of the specific exposures and their prominence have changed over time. We look here at the interactions between environment and humans -- the human-altered environment. Under the physical environment, we're concerned about things like the structures in which military personnel live and work. Some of these are temporary, and some are permanent. Some have good protection from the natural environment, some do not. Weather and climate are another aspect of the physical environment that can effect health. The soil, and vegetation, and water sources in the area in which combat occurs can affect health. And certainly water supply and sanitation are quite fundamental to health. Transportation and communication structures also can affect health because they can affect the rapidity with

which health care is provided.

The chemical environment, of course, is the focus of your conference, and I'm going to speak very little about that in detail because there are experts in these areas that will be giving you considerable detail. Today we're concerned a great deal about carcinogens and toxic chemicals in the water and in the air, as well as directly exposed to military personnel. The sources are both weapon and non-weapon sources.

The biological environment is complex. It includes not only prophylactic drugs, which have produced some health effects, all drugs that we take do have side effects, but it also includes microorganisms, plants and animals in the local environment, and the local ecosystem.

The psychosocial environment needs to be taken into account, not because the health effects are psychological, they are of course physical, but because in everyday life, the kinds of groups we work in and the kinds of social factors that affect our lives affect our health. Social interactions and social support, or the lack of it in the military, can have a tremendous impact on health, and it can exacerbate the kinds of interactions that there may be with these other types of environments. Both the local and the home-based social, cultural, political, legal, ethical, and economic environments also affect health. So, as we can see, the situation is complex. It isn't hopeless, but it is complex.

Another part of history is looking at syndromes and unexplained illnesses. As you probably know, there was a publication recently that was a review of syndromes and unexplained illness associated with war historically. And some common symptoms have been identified. It was shown in this report that the first war in which unexplained illnesses were reported was the Civil War, and the condition was called *irritable heart*.

The kinds of symptoms that we have here are similar to some of the ones that we have seen in Persian Gulf veterans:

- Fatigue and exhaustion
- Shortness of breath
- Palpitations and tachycardia
- Headache
- Muscle and joint pain
- Diarrhea
- Excessive sweating
- Dizziness
- Fainting
- Disturbed sleep
- Forgetfulness

‘ Difficulty in concentrating

In World War I, special clinical and research programs were established to care for those that were affected by these unexplained symptoms and syndromes. Some cases were found to be due to shell shock, which was found to be able to be treated effectively at the front for many cases. The term *post traumatic stress disorder*, which you've heard a lot, came into use after Vietnam. The most extensive clinical and research program into postwar health is that which we see today which has followed the Persian Gulf War.

Now, let's turn to some of the demographics of the Persian Gulf War itself. Demographics affect health because the distribution of disease is not random. It varies according to these characteristics. There were nearly 700,000 people deployed to the Persian Gulf. The distribution in terms of active duty, reserve, and National Guard was about 83% from active duty sources, about 10% from reserves, and about 6% from the national guard. It is known that this was a higher proportion of reserve and national guard than had been deployed in prior wars.

The male/female breakdown was different. There were a higher proportion of women than had been deployed in prior wars. Here we see racial and ethnic diversity which has occurred before. About 68% of those deployed were white, about 23% were black, 3.6% were Hispanic, and those in other race and ethnic groups were 6%. And again, ethnic diversity for a variety of reasons, including cultural factors and cultural habits, are important in trying to understand some of the health outcomes that we see. Culture can affect the impact that something as traumatic as war has on an individual.

The age distribution is different than we have seen in other deployments as well. This was an older population. 26% of those deployed were over the age of 31. From my perspective, not very old, but older than those that are usually deployed. Over half were over the age of 29. Overall, this is an older population than has been deployed in the past.

I'd like to turn now to looking at some of the exposures that have been considered. They are extensive as you know. Trying to identify these and link them to health is not easy. In fact, the most difficult task in any epidemiologic study that is conducted retrospectively or historically is the identification of specific exposures, determining their independent effects as well as their interactions with other exposures, then linking those known exposures to specific exposed populations, and finally, linking both of those to specific health outcomes. The Persian Gulf studies are no exception. So, I'd like to begin by reviewing the exposures that have been considered.

Chemicals, of course, is the focus of this conference. These are just a few of the general categories. Believe me, in the time allotted, I'm not going to be able to encompass everything that needs to be thought about. Pesticides are a major issue. Lindane and malathion and similar

types of pesticides were used for environmental pest control. Uniforms were treated with an insect repellent, permethrin. And personal use of DEET was quite common in areas where insects were more problematic.

Fuels and decontamination solutions are another category of chemicals that were used. They were used in stoves and heaters, and in portable generators, as well as in vehicles. There is concern that in some areas there may have been exposure to lead from diesel exhaust where unventilated heaters were used in living quarters. It's well known that there was extensive smoke from oil well fires, and that the risk from that smoke and the chemicals in them was increased during the winter because of stagnant air conditions. Oil spills were common from many sources, and people were exposed to chemicals from these sources.

There were also what we call "occupational exposures" and by this I simply mean the kinds of exposures that occur when one is carrying out one's everyday duties. These were in a variety of categories. The major ones had to do with repair and maintenance activities, things like:

- Battery repair which produced exposure to corrosive liquids;
- Cleaning and degreasing which produced exposure to solvents;
- Generator repair which produced exposure to carbon monoxide;
- Vehicle repair which always has a variety of exposures including carbon monoxide, asbestos, and solvents; and finally
- Weapons repair.

There also was exposure to depleted uranium which is used in anti-tank munitions and in tank armor. Its major toxicity is not radiation, but rather chemical. At least one "friendly fire" incident wounded 35 soldiers, 22 of whom retained depleted uranium fragments -- 33 of that original 35 are being followed. After 3 years, it was shown that 15 still had shrapnel, but none had evidence of toxic effects.

The Presidential Advisory Committee is clear that there was some exposure to chemical warfare agents, particularly in Khamisiyah.

The next general category of exposures is in the natural environment. When people are deployed for warfare, this of course, is a hostile environment. Not just because of the reason that one is there, but also because the environment is different from what people are normally exposed to. The climates were extreme. Overall the temperatures ranged from 45^0 and 65^0 in the winter to 80^0 and 130^0 in the summer. Most of us come from areas where the temperature range is

considerably less than that, so this was one thing that could easily affect health. Clearly, many people have respiratory problems, and when you're deployed to an area where there's blowing sand, sand which was everywhere and which was powdery, this is going to make respiratory conditions worse. There was also smoke from encampment fires. For those of us who have asthma and other kinds of respiratory conditions, this will make them worse as well.

In some areas, there were inadequate sanitary and hygiene facilities. The original public health schools were called "Schools of Hygiene" for a reason. That's the basis of good health -- simple hygiene. In many cases, there were inadequate shower facilities, latrines that were built early were not adequately designed, and there was smoke from waste fires. Crowded tents made this problem with inadequate sanitary and hygiene even worse.

Sand flies were a concern going in. What was expected were cases of cutaneous leishmaniasis. There were fewer cases than expected. What was unexpected were the 12 cases that were reported of tropical leishmaniasis or visceral leishmaniasis.

And then finally, diet. You may think this is a strange thing to put under "environment," but what happened here was that MREs were used for a longer time period than they should have been because they wanted to keep people unexposed to the local food sources. Because of this, there was inadequate nutrition. The MREs at that time were not designed for long use, and so they didn't have appropriate balanced diet for a longer time period. Also, they're not particularly tasty little morsels, and people got tired of them, and didn't eat them. So, they had inadequate numbers of calories per day. As you may know, the Institute of Medicine has done a report on this specific issues looking at diet and MREs, and from what I've read, new MREs have been developed that at least have adequate nutrition for a longer time period. Whether they're more palatable is another issue.

Another category of exposures or agents is biological. And for the Persian Gulf War, primarily, we were concerned about biological warfare, and so prophylactics were given in the effort to provide some protection to the troops. Pyridostigmine bromide was widely used to protect against organophosphate nerve agents. This is a well-defined drug. This class of agents has been in use since 1864. It can make asthma and heart disease worse. Anthrax vaccination also was widely used, and botulinum toxoid vaccine was used on fewer troops, and this is another drug which is well known to have different effects on men and women. There were some health effects from these, but there's no drug that we can take that doesn't have side effects, and with these as with any others, you have to balance the possible protection against the side effects that do occur.

The final category of exposures is psychosocial, and these are things that can actually make some of the other categories of exposures worse. The number one, of course, is anticipation of combat. The reason that people were in the Persian Gulf was not a friendly situation. It was filled with

tension. Tension of this sort is going to cause many kinds of health problems. There's the normal sort of concern that anybody would have being deployed for war, but in the Persian Gulf War, we had added the impact of media coverage. There was also the fear of the potential for use of biological and chemical warfare agents, which was made worse, of course, by the prophylactic drugs for these specific purposes that were given. There was rapid deployment and rapid reentry to the United States. In both directions, there was very little time to acclimate, and it appears that the programs that were developed were not adequate for acclimation either to deployment or from deployment. These appeared to have a greater impact on reserves and National Guard. Clearly, there would be an effect on one's health when a unit member was injured or killed in a non-combat accident, which did occur. There were gender differences and tensions because there were a larger proportion of women deployed than before. There were just the kinds of considerations that weren't thought about in daily living with men and women living together in crowded conditions. And there are differences in personal habits such as smoking, alcohol, and drug use that do differ for men and women and will interact with other kinds of exposures. These were made worse because there were limited rest and recreation opportunities.

Now, the next one I have here is easy access to and contact with family and friends. This may seem like a strange item to you to put under potential exposures and agents, but in fact what happened was there were two sources of stresses. In prior deployments, military personnel didn't have easy access. They couldn't call their families every week. So, you had the stresses of your daily life of being deployed added to then the stresses that remained at home. Just simply the stress of being separated from family and loved ones. Problems at home, people did not have the luxury of being more detached from those problems. And so, on a daily basis, concerns were brought right to the fore about family issues, problems children were having, perhaps problems with other relatives. And, again, easy access to media accounts of the war created some additional stressors.

In all of these four categories of exposures, we have to think about the individuals agents as well as their interactions.

Next, I'm going to provide an overview of mortality that occurred during the war and after the war. These are deaths that occurred during Operations Desert Shield and Desert Storm, and it includes all deaths among all active duty U.S. military persons for one year, both deployed and non-deployed. There were a total of a 1,769 deaths. 372 of those were among the Persian Gulf deployed, and 1,397 among those deployed elsewhere. The only category at this time of deaths during the war that was significantly elevated among Persian Gulf veterans was the category of "unintentional injuries." All non-battle related deaths were somewhat higher. In particular under the "unintentional injuries" deaths due to aircraft accidents, explosions, and a wide variety of other sources were higher than those in other deployed groups. The category of "unexpected and undefined sources of death" was also higher in Persian Gulf veterans. This category is kind of a catch-all which includes deaths for which there was not apparent preceding illness or injury, for

example, deaths that were attributed to cardiac or respiratory failure and other causes. It is known that there were some areas, some regions in which access to medical care wasn't as readily available, nor was access to emergency medical service.

Looking at deaths after the war, this is a retrospective cohort study of all of the Persian Gulf War veterans and a comparison group of about 750,000 other veterans that were not deployed. They were followed from May 1, 1991 through the end of September of 1993. There were 1,437 deaths among 544,000 men that were deployed to the Persian Gulf, and 70 deaths among 50,000 women that were deployed. Over all, all causes of death were significantly higher for men, but not for women. However, both men and women had higher mortality from causes other than disease and from accidents. Motor vehicle accident deaths, the rate was significantly higher, but for men only. And if we look through the rest of these, none of these were significantly different for Persian Gulf War veterans, but infectious diseases were, in fact, significantly lower.

Looking at hospitalization rates, and again, these studies, none of them cover all of the hospitalizations. This was a retrospective cohort of 547,000 Persian Gulf veterans seen in Department of Defense Hospitals. The one area that was higher among Persian Gulf veterans was neoplasms or cancers, and those were attributable to testicular cancers that were diagnosed during 1991. In 1992, diseases of blood and blood forming organs were higher, the rate of hospitalizations for those were higher among Persian Gulf veterans, and this was due almost entirely to anemia.

Diseases of the genitourinary system were higher, in particular among women, among Persian Gulf War Women Veterans. These were due to infertility, to inflammatory disease of the ovary, fallopian tube, and pelvic tissue, as well as to other disorders of the breast.

And then, there were categories of mental health disorders that were different in Persian Gulf War veterans. As we see at the bottom, neurotic disorders were actually significantly lower among Persian Gulf War veterans, but some of the other conditions were significantly higher. These included drug dependence, adjustment reaction, non-dependent abuse of drugs, and alcohol dependence.

A major concern since the war has been reproductive effects or birth defects. And there is one study published that has evaluated birth defects at a particular time and in particular situations. The study that I show you here reports all live births in 135 military hospitals for the years 1991 to 1993. So, it is limited to those years, and to birth defects that were detected in the hospital. During this time, there were 33,998 infants born to Persian Gulf War veterans, and 41,463 born to other veterans. Of these, 30,000 were born to wives of 29,000 Persian Gulf War male veterans. 32,638 were born to wives of non-Persian Gulf War male veterans, 3,800 were born to 3,700 Persian Gulf War women service members, and 8,800 were born to 8,400 non-Persian Gulf War women. So, we're looking here at birth defects among men and women separately. And there is

an error on that slide. The second category of congenital hip dislocation is higher in Persian Gulf War veterans, but it is not significantly higher. Overall, severe birth defects were not higher among children of male and female service members. There were, however, significantly more births among men and women Persian Gulf War veterans than for others. It's important to keep in mind that this is not a comprehensive assessment of birth defects, but rather, only the birth defects that were seen at birth. There are many that are not seen for months, 3 to 6 months afterwards, and some don't appear until a year later. In many cases in reproductive epidemiology, we know that the most severe birth defects are, in fact, never known because they produce spontaneous abortion. So, in fact, we can't really measure all of the birth defects that may have occurred.

There are many regional studies that are being done of either veterans in groups of states or individual states. On this slide, I'm showing you some of the data from an interesting study that was done among New England veterans. This is a cohort of 2,949 members of the Fort Devens Reunion Survey. These include U.S. Army active, reserve, and National Guard that were deployed to the Persian Gulf. The initial survey, this is a unique one because the initial survey was done 5 days after return. The second survey, and the data I have here are from that second survey, were done 18 to 24 months later. About half the samples surveyed reported no symptoms, but about 13% reported 5 or more symptoms. Those that had higher numbers of symptoms were more likely to be reserve and Guard, they were more likely to be women, they were more likely to be unemployed at this time, and to have drug and alcohol problems. They also had higher rates of combat exposure. The symptoms shown here are general symptoms such as general aches and pains; being overly tired and having a lack of energy; headaches; difficulty with sleeping; being nervous or tense; having a depressed mood; having difficulty concentrating; experiencing upset stomach; having common cold or flu; muscle twitches or trembling; skin rashes; a loss of interest in normal daily activity such as being with friends and watching TV, movies or news; shortness of breath but not when exercising; and rapid heart rate.

Another study that I haven't shown you here, we'd be going on for days if I tried to review them all for you, was a telephone survey of Iowa Persian Gulf veterans. That telephone survey did show some similar kinds of results. This included Active, National Guard, and reserves as well as those from non-Persian Gulf sources. Their findings included a higher prevalence of Persian Gulf personnel reporting symptoms of depression, of post traumatic stress disorder, of chronic fatigue, of cognitive dysfunction, of bronchitis and asthma, of fibromyalgia, of alcohol abuse, and sexual discomfort. A quality of life survey that was done in these veterans found diminished mental and physical function scores for the Persian Gulf veterans. There were larger differences in the National Guard and reserves than in others. In addition, those who spent time in Iraq, Saudi Arabia, or Kuwait had higher prevalence of depression, fibromyalgia, and cognitive dysfunction than those deployed elsewhere in the Gulf. Now, of course, these regional surveys can't represent the entire deployed group. On the other hand, if we have enough of them, they may begin to give us an idea of where there's consensus.

The Persian Gulf Registry offered another opportunity for veterans experiencing health problems to seek diagnosis and care. This published report included 74, 653 of those voluntary participants. There are over 100,000 participants in the registry today. This is open to anyone who is no longer on active duty and deployed to the Persian Gulf. Clearly, there won't be anybody in this group who is without symptoms because people join the registry because they're seeking diagnosis and care. People who did participate in the registry were more likely to be from Army, the reserves, and National Guard. They're also more likely to be over the age of 30, and to have served directly in the Gulf War theater. Of all of those in the registry, nearly 23% were not able to get diagnoses for their symptoms. Some of the more common symptoms that were seen were pain in the joint, psychologic and other adjustment reactions, asthma, essential hypertension, migraine, malaise and fatigue, and sleep disturbances. So, these are some of the same kinds of symptoms that we see in the regional reports as well. As a voluntary kind of data source it, of course, is not going to be representative and not as useful as we would like it to be for research.

Now, I did indicate that people in the United Kingdom and Canada have done some similar kinds of survey, and this helps us understand again where we might have consensus in health outcomes if we see similar results from studies in other areas. The survey in the United Kingdom also found certain kinds of health effects that were higher among Persian Gulf veterans. This was a mailed survey of a random sample of male veterans – 4,248 male veterans compared to 4,250 Bosnia Veterans and 4,246 non-deployed era veterans. They were asked about deployment, about exposures, about symptoms, and about illness. The response rate was around 65% which is excellent for a mailed survey. The average response rate, just to give you a comparison in mailed surveys is around 18%. The response rates were the same for each of these 3 cohorts. Some of the symptoms that were reported that were in excess in the Persian Gulf veterans were feeling unrefreshed after sleep, irritability and outbursts of anger, headaches, fatigue, having sleeping difficulties, forgetfulness, joint stiffness, loss of concentration, flatulence or burping, pain without swelling or redness in several joints, feeling distant or cut off from others, avoiding doing things or avoiding certain kinds of situations, chest pain, tingling in the fingers and arms, and night sweats. This is a recent report. It was just published on January 16, 1999, in *The Lancet*. The authors conclude that the health problems among these United Kingdom veterans were over and above those associated with deployment to an unfamiliar hostile environment. They also say there may be some link between illness and vaccination against biological warfare agents for some of these symptoms.

Conditions that were reported in this United Kingdom survey included back disorders, hay fever, dermatitis, sinus disorders, migraines, diseases of the hair or scalp, sexual problems, asthma, and chronic fatigue syndrome or myalgic encephalitis. They also report in this study that, in spite of the elevated symptoms and diseases, disability was not severe and there was no impact on other outcomes such as employment and marital relationships. The authors conclude, and I quote, "We believe that our data constitute firm evidence that service in the Gulf War has affected the health of service men." They have not been able to link these health outcomes to either general or

specific exposures.

The Canadians have also done some studies of health outcomes, and these were reported in 1998. In their studies, it was a mailed survey again, of 3,133 Canadian Gulf War veterans, and 3,439 comparison Canadian Force Personnel. They had a response rate of 73% for the Persian Gulf veterans and 60% for the comparison Canadian Force group. They also used comparisons with the general population with the 1990 Ontario Health Survey. The Canadian Gulf War veterans had 6% women and 94% men, and the mean age was 38. So, they also had a force that was somewhat older than we've seen in previous deployments, and had a higher proportion of women. The problems reported that were higher among Persian Gulf War veterans included hay fever and other allergies, back pain, serious bone and joint problems, skin and allergy diseases, digestive problems, arthritis and rheumatism, high blood pressure and hypertension, emphysema, chronic bronchitis, and chronic cough. The Canadian Gulf War veterans also had a higher prevalence of reduced activity and reporting life as stressful than the Canadian Force controls. They had a higher prevalence than the population controls of reduced activity days and visits to health care practitioners. This was found both in short-term and long-term problems. The authors comment on the unique stressors of this war, namely the threat of both chemical and biological warfares.

Other health outcomes that were seen in the Canadian Force personnel that were higher than the comparison personnel in Gulf War veterans included cognitive dysfunction, chronic fatigue, fibromyalgia, diagnosed post traumatic stress disorder, post traumatic stress disorder symptoms, major and minor depression, chronic dysphoria, respiratory disease, bronchitis and asthma, anxiety, and multiple chemical sensitivity.

Now, for the next few days, you're going to try to figure out where we can go from here. And so I'd like to comment a little bit on where we can find leads. Fortunately, we don't have to start from nothing. We can find leads in many different places, and prevention has to be the key. There's no questions that we have seen health effects from war historically and that we're going to continue to see it in the future. As war becomes more technological, the health effects may become more prominent. We can find leads in the civilian population in primary care. This will be extremely important because it can tell us what health effects that were seen in deployed personnel that are similar to those in the civilian populations, and perhaps more importantly, which ones are different and unique to the military experience or occur at higher levels among military in general or among those who are deployed. We can get leads for the most traumatic situations from civilian population from disasters – things like tornadoes and hurricanes and things that we hope aren't repeated like the Oklahoma Federal Building bombing. These produce the same kinds of severe trauma and have effects on the civilian population that are also seen in warfare.

Disease surveillance is going to be extremely important, and it's an area that needs to be improved. There are outstanding programs here at the Centers for Disease Control and

Prevention and also at the National Institutes of Health. They could be models for the military system. Prevention programs abound everywhere these days, everywhere from our local, county and city health departments to state health departments and the National Institutes of Health and Centers for Disease Control and Prevention. Many of these are programs that can be used directly by the military or at least can be used as models. In epidemiology, we're going to get the best leads from occupational and environmental research because we'll find leads here for research into specific environmental exposures that we know lead to specific health outcomes. And in prevention research we're going to be able to get leads for reducing morbidity and mortality from illness in future deployments.

A major component of prevention is surveillance. That has been a problem for the Persian Gulf War. We didn't have extensive or useful baseline data. In the future we're going to have to have baseline and ongoing measures for all military personnel and special measures and exposure data linking that between the Department of Defense, Veterans Affairs, reserves, and National Guards. The linkage is critical. Each of these agencies has some sort form of surveillance and some form of data. For the Persian Gulf War we saw that those are not necessarily linked, they don't collect the same kind of data, and it hasn't been easy to follow people from one status to another.

Research is needed in many areas to define what can be done in the future as well as to try to further define what has happened with Persian Gulf. We need to conduct research into gender differences in pre-deployment, deployment, and post-deployment health. It became quite clear in the Persian Gulf deployment that there wasn't adequate or appropriate health care for women who had been deployed. And we need to understand what the gender differences are going to be in health outcomes in the future. We need to conduct research into preventive strategies, not only for biological prophylaxis, but also for group cohesion and support – what can be done within group situations, particularly with a different mix both in terms of age and gender that will make this a more supportive kind of environment? We also can take appropriate general preventive services and use those and develop research in those areas. We need to have research into the interactions. That's the most difficult area. Even when we can tie down specific and individual exposures and understand the health effects, we don't know to what extent those were made worse by other kinds of exposures. So, we need to do research that looks at the interactions between military medical products and other drugs and other chemicals, as well as operational stressors. And we need to conduct research into somatic or physical consequences of psychological stressors.

We need to develop better methods to assess exposures to non-threat chemicals, and to reduce or eliminate those exposures where ever they're possible. Research specifically is needed into the health outcomes that are specific to deployment of reserves and National Guards. We may need special programs to reduce the health effects of deployment for these populations. And we need to conduct research into symptom based illness. We need to understand what the causes are, what the short-term/long-term consequences are, how to provide appropriate care, and how to

develop prevention.

As a researcher, you're going to expect me to tell you we have to do more research. But we can also do interventions today. What can we do now? Well, we can begin by providing information and education about health risks, about general personal lifestyle concerns, as well as occupational exposures that occur in the military. That's only the basis for other kinds of action. From there, we need to move on to specific prevention programs which are both pre-deployment and post-deployment and focused upon health. These can be tailored to specific lifestyle habits such as smoking and alcohol use, and they also can be tailored to specific occupational exposures over which individuals don't have as much control. We can develop pre-deployment, deployment, and post-deployment prevention programs that are focused on issues that are specific to each kind of deployment. Something will be known about every future deployment about the environmental and other kinds of health threats that will be there. Once we identify those exposures, we can develop prevention programs in advance. These include occupational and environmental types of exposures as well as known and expected warfare exposures. From this we can improve both medical and non-medical counter measures. An important part of prevention is going to be having improved health services for women in general, and improved health services for veterans and their families after deployments.

An important component is infrastructure which is needed to support prevention programs, surveillance, and research. This includes coordinating surveillance and prevention activities across the branches of the Department of Defense and between the Department of Defense and the Veterans Affairs. An idea, but I think perhaps more realistic approach, will be to develop and implement a single, uniform, continuous, retrievable electronic medical record for each service person. To date, the different branches of service and Veterans Affairs have different medical records with different codes for the same entry. It is difficult, if not impossible, to follow people and compare them over time. Not only do we have to have that uniform across the branches of service and Veterans Affairs, we have to improve linkages among health information systems in the community. Not all medical care for military personnel is provided in Department of Defense facilities. Some of it is provided in the community. If we're going to realistically follow people over time, we need to have this linkage. And we need to coordinate the agency research programs so that studies aren't done on the same topic, but in different ways, or in non-comparable ways.

Within the military service, it's going to be important to strengthen the capability of Armed Forces in epidemiology, preventive medicine, and public health. We saw in studies of the services right after the Persian Gulf War that, in fact, these very areas of expertise and personnel that are needed most now have been reduced. So those will need to be increased over time.

As an academic I can tell you we need to integrate military, medical and public health priorities into academic programs and public health and health care. I am a graduate of Johns Hopkins

School of Public Health, and when I was a student there, there was virtually nothing in the agenda, in the curriculum, about military medicine or the difficulties of health after war. The Johns Hopkins University now has a Center for Bioterrorism which is focused not just on military conditions. But I think we need to be more thoughtful and to train our students to understand the public health effects, things that we may see in everyday life in civilian situations, perhaps will be exacerbated in the military situation, and we need to think about those and train people specifically to deal with these issues.

Finally, there are scientific issues that are going to have to be addressed in future studies. Some of these I have shown here. These include the baseline health assessments. It's not just that we have to do them, but they have to be complete. They have to be objective and include physical exams, and they have to be representative and ask the right questions. We need to have quantitative and objective measurement of exposures. This is critical for linkage to prevention and linkage to health. We need to identify relevant exposures prior to deployment. This may be difficult, but it is possible and it needs to be done to the extent that it can be done. And we need to understand the interactions among physical, chemical, and psychosocial exposures. These can be done independent of deployment. This kind of research needs to be increased tremendously. We need to have objective measures of post deployment health, including representative sampling, appropriate outcomes, and use of clinical exams, medical records, and laboratory tests. We need to identify relevant outcomes prior to deployment. Not only relevant exposures, but relevant health outcomes. What do we know is likely to affect health? Some of these are well known before deployment occurs. And then we can identify approaches to preventions. We need to establish priorities for effective prevention measures both prior to and during deployment. Prevention is the key.

In conclusion, we know that health effects of war have existed since the human race has utilized combat to settle differences. Readiness must include public health and prevention if we are to reduce morbidity and mortality for deployed forces. No individual study and no individual prevention program is perfect. But a comprehensive approach identifying relevant exposures, health effects, surveillance, and prevention will move us in the right direction toward protecting military and deployed personnel from future adverse health effects.

Thank you.

Dr. Richard Jackson

Thank you very much Dr. Swanson for a panoramic overview. That was a lot of homework. Our next speaker and moderator, actually, is Major General Donald Edwards, United States Army retired, who is the Special Projects Coordinator for Congressman Bernie Sanders. Don, why don't you come on up just in the interest of time, and would you like me to introduce your panel or will you? Okay. At the same time, I'm going to ask the panel to begin to come up as well.

Don Edwards is the Special Projects Coordinator for Congressman Bernie Sanders, and is Congressman Sanders' Principal Assistant for Gulf War illness and all other veterans' issues. He is a retired U.S. Major General and served 2 tours in Vietnam, earning 8 campaign stars. His decorations include the Legion of Merit and the Bronze Star.

The Experience of Veterans (Panel Discussion)

Donald Edwards
Major General, United States Army (Ret.)
Special Projects Coordinator for Congressman Bernard Sanders
Burlington, Vermont

Please, if you're on the panel come forward. I'm not going to give any speeches. I want to get the panel going here. This should be about the veterans, and I want the veterans up here so they can have a word with us. Grab a chair or two. Just really quickly, I'm Don Edwards. I'm Bernie Sanders' Special Projects Coordinator. I've been working on the Gulf War illness issue with Bernie now for the last 2 years. I'd like to only say a couple of things. It's a real pleasure for me as a Vietnam Veteran to be here and to assist my comrades from the Gulf War. As they know, we wrestled with the Agent Orange issue and are still wrestling with it. In fact, it's one of the things that Congressman Sanders hopes to reopen in the current session. It's also a source of great satisfaction to me that the VVA, which was founded in Vermont, the Vietnam Veterans of American Chapter 1 in Rutland is the host of the Gulf War Resources Center. It's no accident that so much good legislation got passed last year. The energy of Congressman Shays and Congressman Sanders is supported by a staff. I happen to be a Vietnam Veteran. Bob Newman is somewhere in the audience, Bob where are you? Stand up please if you're here. Bob is a Korean War Vet and it's no accident that another close ally is Jim Tuite who's wife is on the staff of Senator Byrd who played a very key role in getting the Gulf War Exposure Act passed, legislation that was drafted by Chris and Bernie, and the ban on practice of experimental medicine on troops without the specific written permission of the President. Jim Tuite was a corpsman in the Vietnam War.

We have a very short time. We have 45 minutes for 11 people. These are the most important people in this room – the veterans. And these are their representatives. And folks, what I'm going to do is have a really severe bell at about 3 minutes which will give us about 10 or 11 minutes to have a discussion. I'm not going to be an arbiter of who is more important, I'm just going to go down this thing. The CDC folks put this together alphabetically, so I'm going to start with Mr. Hardie, please.

Anthony Hardie
President, Gulf War Veterans of Wisconsin
National Secretary, National Gulf War Resource Center

Madison, Wisconsin

I listened to Congressman Sanders this morning, and Congressman Sanders has been a great ally of Gulf War veterans for a number of years. It is unfortunate that we still don't have studies, epidemiological studies that are showing exactly what's going on with Gulf War veterans. And we discussed, some of the research that was just presented a few moments ago, was discussing some of the symptoms of the experience that are exactly the problems that veterans have been complaining about. When Congressman Sanders read from the Congressional report that stated that the VA and the DoD have "mistaken motion for progress," those same reports that that Congressional committee was harshly criticizing are still the existing research on the epidemiological side. It's unfortunate that that's the case. Obviously that's very flawed when we're looking at, for example, birth defects among veterans. We're looking at military hospitals. Most Gulf War veterans are no longer in the military. That's certainly going to be very flawed.

Now, we were discussing some things last night among some of us veterans. It seems very important that we take a look, that what we hope for out of this conference is a 2-fold approach. We really hope that research will be geared towards looking at the effects of what is actually happening to Gulf War veterans, and we also hope there will be research simultaneous to that as far as what the causes are, the potential causes, all the different factors that we've been discussing already this morning, and what the potential illnesses are related to those. Eventually, Gulf War veterans, we need to get our health back. Some veterans are too sick, in fact many are too sick be here. Many are still out in the audience here. It's very important that we focus on what those health issues are. All the different, not just the sleep disorders and those kinds of things, but the gastrointestinal problems, the respiratory problems. All these sorts of problems that are plaguing us, some that are mildly disabling, some that are very seriously disabling. So, again, we hope that the research will focus on those 2 aspects, both on the effects of what Gulf War veterans are experiencing and how to deal with those effects and the treatment and so on, and second with the potential causes of the known hazards and what those known hazards will potentially lead to. Thank you.

Mr. Donald Edwards

Thank you sir. Rick Hirst.

Rick Hirst
Training and Quality Control Specialist
Veterans of Foreign Wars
Washington, DC

Thank you very much. Good morning. I am the National Training Officer for the Veterans of Foreign Wars Washington Headquarters. Prior to that position, I worked for the VA. I retired from the VA in September of 1997 at which time I was the Chief of an advisory review staff which instructed VA personnel how to work many claims including Persian Gulf. I tried during my VA career to get the message and policy out to the regional offices, and it's debatable at this point whether they understood everything we were trying to say. The VA continues to fight many, many problems, one of which is the quality of their decisions.

My expertise is in benefits. So, I'm a novice to this area of research. But, I can tell you from a personal standpoint, although I am not a Gulf War veteran, I have a son who is. And he's very healthy today, but I would sure be interested to know if anything's likely to happen to him in the next 20 years 'cause he's got children of his own.

I represent an organization of approximately 2 million people. We are celebrating our 100th anniversary in 1999. That's an awful long time for an organization to be in existence. We have, we believe, stood for veterans' rights throughout that time. But like any statement that you make or mission that you perceive, sometimes the focus gets lost. So, I'm here to tell you that during our year of celebration, our hierarchy, including our Commander in Chief, Tom Pouliot, intends to refocus our efforts on advocacy and veterans' rights. This may appear to be confrontational with VA, but I think at this point in time, we have reached the situation where we should be involved in the agenda rather than reacting to the agenda.

We have created what initially started out as a health care help line: 1-800-VFW-1899. We take incident reports from veterans, from friends of veterans, from the general public asking us many, many questions and bringing many problems to our attention. It initially started with health care system problems, but the benefits questions have been increasing, and the Gulf War questions seem to focus on 3 basic issues, and I would like to say that we as an organization support the use of depleted uranium because of its effectiveness on the battlefield, but we think that the jury is a long way from coming back as to what is likely to happen. We are a strong supporter of continued research in DU. We also think that there is some evidence out there of birth defects, and we want to push for birth defect [research]. But the one specific condition that seems to be, I hate to use the word "prevalent" but it's noticeable, a number of veterans have complained about Lou Gehrig disease, ALS. We feel there is sufficient information out there to warrant research. And that's one of the things we will push during the coming year.

I urge any of you who have any questions to please call the hotline. We will try to help you in any way we can. And with that, I will be available for any conversations during the next couple of days. Thank you very much.

Mr. Donald Edwards

Do you want to give the number of the hotline again?

Mr. Rick Hirst

The number of the hotline once again is 1-800-VFW-1899. Thank you.

Mr. Donald Edwards

Thanks Rick. Debbie Judd.

Debbie Judd, RN, MPA/HSA
President, Northern California Association of Gulf War Veterans
Board Member, National Gulf War Resource Center
Valley Springs, California

I'd like to commend the CDC for this approach of a conference to research. What I've basically spent the last few years doing since I've not been able to work as a nurse since returning from the Gulf War, is that I've been working as a Veterans' Advocate. And I've interviewed thousands of veterans, and in doing so have tried to identify a symptoms list. What I've seen across the board is that your veterans are truly very good historians. They can tell you what their symptoms are, and from coast to coast you tend to hear the same thing coming out of the veterans' mouths. So, what I would recommend in all the research projects is that you use the veterans. They are truly your best resource in lieu of textbook theories. The other thing is that repeatedly we've had them asking for a single cause. What we tend to see now is that there isn't a single cause, but rather a combination of causes, and as long as we continue to look for that single cause, nothing will be done.

This year, at this point, 8 years after the war, I've seen a shift in what the veterans have asked for. Initially everybody wanted to know what the cause was, why they were sick. At this point, I hear a lot more of, "What can they do to treat it?" What that does basically in research is that it reverses the cause and effect role, and veterans are looking for now something just to slow down the deterioration process.

Again, like I said, I think that your best resource is to keep the veterans involved and let them play a part in the research.

Mr. Donald Edwards

Thank you Debbie. L.A. McClure.

L.A. McClure
Referrals Coordinator
Alaska Gulf War Syndrome
Eagle River, Alaska

I'm a Gulf War syndrome Referrals Coordinator. This is a clean slate start you might say. Over the past several years, we veterans have been anxious to find some treatment or some answers to our problems and we've basically been treated as if we were malingerers, or suffering from stress. And I think we know enough about stress to know what that is. But we don't have, still, some concrete answers. We are guardedly optimistic with this start by the CDC for yet another fresh approach to looking into these issues. We need a case definition for Gulf War illnesses. We don't have that yet. We need to turn the prevalence, association and causation around. Instead of causation, prevalence, and association – turn it around. If we can find a cause, wonderful. But if we're going to aim so high up for **a** cause that we overlook that we have a prevalence, and we have an association, and we ignore trying to identify those things to help veterans for today, not for 20 or 30 years from now, but in the present time frame, then I think we can get closer to helping the veterans' needs today. We'd like to get well. I realize that's a big order.

But the credibility with the VA and the DoD was lost. We don't want to lose this opportunity to find some answers. How do we go about that? I'd like to suggest that you maintain a research review panel of veterans such as what we have here, or in some fashion that we can stay in step with whatever is being done. So much of previous research was done in ways that we found flaws, errors in the methodology. We would like to try to avoid that. My time is up? Thank you very much for being here.

Mr. Donald Edwards

Thank you very much. You were doing extremely well on your time, by the way. Ron Murray.

Ronald Murray
President, Gulf War Veterans of Georgia
Board Member, National Gulf War Resource Center
Atlanta, Georgia

Good morning. As President of the Gulf War veterans of Georgia and a board member of the National Gulf War Resource Center, I'm going to speak to you on kind of a personal note. From

listening this morning and hearing some of the comments that have come out as far as research, it's just like deja vu, it's just like, "Well, nobody's going to believe you." Well, for the people in the private sector who don't understand, like if you go to a physician expressing your symptoms, tell him what's wrong, they generally will normally look at you like, "Well, you're mistaken in what you feel. You're dreaming this." Well, we're not dreaming this.

On a personal note, people will not listen to you from the employment side of the house. People are reluctant to talk about their experiences and what they witnessed in the Gulf. The sad part is that I went formally on the record in my law enforcement career, and now my 18-year career is trashed. So, I'm having to completely restart my life, which is very difficult. But, January 19th of 1991, we had an event occur in Saudi Arabia that people denied ever occurred for so long, which was the exposure of an agent in the battlefield, and which was later confirmed by the French as well as the Czechoslovakians. I was given a little business card by one of the Czechoslovakian Commanders in Chief who said, "Here, hold on to this business card. One day it's going to come back, and you're going to thank me for giving you this." And sure enough, it has. So, one thing that I can tell is just that people who have experienced it, that have been out there first hand, they're going to, you know, live the experience. But once they get out of this, get back into their role models as civilians, you know, people that have been traumatized, speaking to Veterans who were in Vietnam, they don't want to talk about this. It's something they want to put behind them.

In today's age, we want to know answers. We have so many means at our disposal right now, and we just have to take advantage of it. But first, we have to listen to the people that have been there. People have to be open and you have to be willing to latch on to that individual or group of individuals. Find a starting point and let's take off from there. I mean, for us that do have the symptoms, we can't change that. We were asked to go serve. We served. I was proud that I served. Unfortunately, I'm a casualty of serving. But I'm not going to hold that against anybody. You know, I'm proud of my service. But we need to take care of our veterans. This is a starting point here, and hopefully, you know, with you help we can go someplace. Thank you.

Mr. Donald Edwards

Thank you Ron. Denise Nichols.

Denise Nichols, RN, MSN, MAJ, USAFR (Ret.)
Vice-Chair, National Vietnam and Gulf War Veterans Coalition
President and Founder, Desert Storm Veterans of Rocky Mountains
Wheat Ridge, Colorado

Good morning. I look out here and I wonder, "How did we get here?" Well, we went to war and it's real. And I'm going to ask openly at this meeting that I know that there's material out there

that we still cannot get as veterans, and the answers of exposures, and they are multiple. Whatever we need to do, if we need to grant immunity, whatever process we need to have the truth come out of what else they know, we need it. We need it for you all to be effective. We need it to cut down the waste of research money. This is real, and that's what I want each of you to understand. It is not stress. It is real damage to the body, and you've got to look at it.

A law enforcement officer, a couple of nurses here out in the audience that served with us, we cannot function because of the memory problems and the fatigue. It's not something we wanted. But we were your patriots. We were out there putting our lives on the line. We need that data out. We don't need to be wrapped up in exposure data and fault finding. Decisions were made that needed to be made at the time. They thought they were right at the time, and they were probably right at the time. But you find out other things that complicate the situation. But we must have that material now. It's 8 years. We have lost people. The mortality rate, think about your truck drivers, your transportation people out in the Gulf. They are trying to maintain their families. And they get out and drive 18-wheel trucks that are on the roads with each of us. We get lost, we get disoriented, we have visual problems. This is a safety factor. Law enforcement, I've had my vets tell me that were law enforcement that they were leaving their gun and forgetting where they left it. And they were dealing with prisoners. This is not safe, healthy, for other people around us. Not just for our family, but for those other people. Pilots, we have pilots over there that are affected. They're trying to keep maintaining their families. This denial has to stop. It has to stop from the head all the way down. If you have memory problems, and if you have visual problems and you're trying to keep going to support your family, you're putting other people's lives at risk. It's just uncalled for.

We've got to get started here. I've called for this ever since I started out going to Washington in '94, to come together, to sit down together. This is the best meeting that we've had of that sort. But, we've got to move rapidly. It is real, it's an, "Oh my God, it's real" situation. We need our commanders, the people that were over us in the Gulf, to find a way, if you need immunity, whatever you need, tell us. We'll go pound the halls of Congress to get a law, whatever's needed. But this is real. This is the lives of your soldiers. It is lives of civilians. And if we cannot face it with us, how can we prepare our civilian population for potential terrorist attacks? We need the treatments now. Right now. Thank you.

Mr. Donald Edwards

Thank you Denise. Matt Puglisi.

Matthew Puglisi
Assistant Director, Gulf War Programs
The American Legion
Washington, DC

Thanks Don, and good morning to everybody, and welcome to all the Gulf War vets and other veterans and family members in the crowd. Welcome to the researchers and investigators who are here. I want to thank you all for the work you've done into investigating Gulf War veterans health since the Gulf War, and the work you're about to do at this conference. It's important work, and I encourage you to dive right into it and play nice with each other. At academic meetings, I think it's more aggressive, not necessarily violent, but pretty aggressive, almost like a war itself when you researchers get together and start to fight about your research. I do want to thank CDC, and especially Drue Barrett, who is an antidote to that perception that government bureaucrats don't really care, and just shuffle them along. This is a product of her hard work, and she's brought a whole bunch of diverse people together, and she deserves a lot more credit, better than your average person who works for the government.

With the time I have, I'd like to make 3 quick points. First of all, Debbie Judd hit the nail on the head. Clinical trials and understanding how to treat these illnesses are what veterans have needed since the end of the Gulf War, and what they especially need now so long after the war. It's what they deserve. The second point is that rigorous scientific inquiry into the very controversial subjects that are related to multiple chemical sensitivity are what veterans and families deserve, and they deserve no less. And lastly, shoot straight. There's a lot of grant money out there perhaps in not rejecting the null and thinking you've found something, especially when it relates to Gulf War veterans' health. But it doesn't help the veterans or their families to do that. If there's no relationship between Toxicant A and poor health outcomes, or some sort of exposure, and there's just not much to it – let's go ahead and walk away from it. Let's try to narrow the field so we can better understand what sort of things veterans were exposed to in the Gulf are related to their poor health that they have today.

And, one final comment, given the state of the world today, and the proliferations of weapons of mass destruction, and chemical weapons, and biological weapons, and the fact that it seems to be only a matter of time before terrorists use these sort of weapons in the U.S., there's a broader population, the U.S. population who can learn an awful lot from an investigation into these agents and their health effects, because, I hope not, but it seems like it's only a matter of time before we're looking at civilian populations in the U.S. that have been exposed to these things, and to try to understand their health after those exposures. Thank you.

Mr. Donald Edwards

Thank you Matt. Victor Silvester.

Victor Silvester
International President
Operation Desert Shield/Desert Storm Association

Odessa, Texas

Ladies and gentlemen, thank you for being here. We appreciate it. Operation Desert Shield/Desert Storm Association started gathering information on the illnesses of the Gulf War in November, 1990. And we have done so ever since. This is not a new issue. This is not a wonderful discovery. The diseases our vets were exposed to have been known about, studied, researched, worked (i.e., the infectious diseases, leishmaniasis, etc.) since the late 1800s. This is not new. Chemical/biological has been studied and researched by honored people such as yourselves since 1914-18, the mustard gas experiments. Everybody's done this part. Everybody's fought this. There is nothing new on this basic foundation. You all know the knowledge. We have been requesting this information ever since 1991 when our first injured soldiers got sick. We have got the documentation. We have seen the reports that DoD and VA have. I announce to you today that DoD and VA stand with no credibility as far as the Gulf War community veterans and their families stand, and will never have.

Ladies and gentlemen, the future of this nation and the future of the vets from the Gulf War are in your hands. You are the people who are going to select and develop the programs that will give us a healthy military in the future which will protect the democracy and freedom that we enjoy. Without healthy soldiers, we cannot fight for freedom and democracy. The CDC has provided us a train built on the foundations of previous knowledge. We are on the right track. We just have to figure out which station to get off at. That's your job. I think each and every one of you today for becoming part of the A Team. Our future, our families' futures and the future of this Nation as a standard shining star of freedom and democracy, is in your hands. I thank you for it, and please be gentle with us, and save us. Thank you.

Mr. Donald Edwards

Thank you Vic. David Smith.

David Smith
State Commander, Idaho Desert Storm Justice Foundation
Lewiston, Idaho

Good morning ladies and gentlemen. Thank you for coming here. It's nice to see all these people here interested in veterans' medical problems. My expertise is that I am a VFW Service Officer. I'm a veteran of the Gulf War. I am 100% service- connected from my service in the Gulf. I've been through numerous studies for the VA and the CCEP to the Gulf Registry. And through all this time I couldn't, even though I kept coming up with things wrong, it was hard to get the VA to listen. And now with all you researchers out there, the VA has to listen to us.

My biggest thing is to help the veterans. I don't know the politics side of this. I just know what

the veterans need, and I know that depression and stress are aggravating our problems by the VA turning us down, saying "no" all the time. Stress is starting to build up, and it does cause problems, and it does lower our immune systems. I know if we don't get this trust built back, there's going to be a problem down the road. I know I'm 35, there's people older in here. We're not going to want to go to war to protect our country. We need a system where when the soldiers go to war they're going to get taken care of. Because I know when we went over we didn't say, "We're not going to fight unless you do this, this, and this." We just went and assumed they'd take care of us. They didn't do it. That's about all I have to say. Thanks.

Mr. Donald Edwards

Thank you David. Debra Smith.

Debra Smith
Vice President, National Gulf War Resource Center
Lewiston, Idaho

Good morning. I'm the Vice President of the National Gulf War Resource Center. We are a coalition of grassroots veterans' organizations that have come together under an umbrella to disseminate and share information regarding Gulf War illnesses. Today I have heard the word "prevalence" spoken many times. It's an amazing thing because I just got off of the phone with a reporter yesterday who mentioned the exact same things. He's doing a follow-up on 8 veterans that he gathered together 2 years ago to do a story upon. Out of those 8 veterans, 1 of them is sitting in prison due to a murder that he committed, an act of rage that he has no memory or recall of. Many of the other veterans among those 8 are very ill. One of them he cannot find. But, out of the 6 of them that he talked to, there was a prevalence. There were vision problems, there were dental problems, there were miscarriages, there were birth defects. Prevalence is extremely important, and where we find the prevalence is talking to the veterans, their family members, their parents, their employers. The signs and symptoms of Gulf War illnesses are just not seen within the veteran themselves. They're seen within the workforce, within the public, and within the home life. Talk to the spouses, talk to the children, find out what it's like when the father does walk down the laundry aisle in the grocery store. Find out what rapid transit is, how these chemical sensitivities can actually limit one's life. Talk to the children about the inactivity that a father or mother who is ill experiences, how they cannot go out and enjoy the normal things that a healthy family does.

Prevalence is the bottom line. This is what is common thread. The common thread is apparent in almost every Gulf War veteran and their family members. It may not be the same symptom, but you'll find them repeated over and over again. Once we find that prevalence, then we can go to the cause. The association is there, but all the facts have not been gathered due to the fact that the Gulf War veterans have been ignored in their outcry of what is wrong with them.

So today, I'm just asking that the Gulf War veterans are continued to be involved in these issues, that you use them as the evidence. They are the evidence. There is no more evidence. It was destroyed. It was lost. We cannot ever recreate the scenario of the Gulf War again – not in a laboratory and not to repeat it again. The veterans are the information, they are the evidence of what happened during the Gulf War. Thank you.

Mr. Donald Edwards

Thank you Debra. Joseph Violante.

Joseph Violante
National Legislative Director
Disabled American Veterans
Washington, DC

Thank you and good morning. I hope that when all of you leave here and go back to your research projects that you remember what was accomplished here. And I hope that you all are paying attention to, particularly, the Gulf War veterans who have experienced these problems and who are having problems. I think a lot of them are visible problems. You know, one thing our country does is ask its military men and women to give 150%, and all veterans did that when they were in the military. They come back, and when they seek their government's help, they find that it's not always readily available to them. This is not unique with Gulf War veterans. It happens with all veterans. But what is unique with Gulf War veterans is that when they overcome the obstacles of gaining access to an overburdened VA health care system, they find that there are no answers to their problems. They find that they are unable to understand what they were exposed to and how that may be affecting their lives today.

This morning, Representative Sanders gave all of you a charge, and I hope in all sincerity that you accept that charge and that you give these men and women 150% of your time and efforts, because they truly deserve it. And I hope that we can get answers. Because they need answers, not today or tomorrow, they needed them yesterday. And, again, I thank all of you for being here and I hope that when obstacles are placed in front of you with your research projects, and people say that, "No, you're looking at this the wrong way" or "No, your research isn't resulting in the answers they want," that you move forward anyway and try to find out what it is that's causing these severe health problems for Gulf War veterans. Thank you.

Mr. Donald Edwards

Thank you Joe. We have a few minutes left. Does any member of the panel have anything they'd like to add at this point? Go ahead Denise.

Ms. Denise Nichols

Very briefly, one of the things we've mentioned is that the vets need to be involved in this research, not as subjects or patients, but we're the double check on the truth and accountability, and validity. We can look at a research study, even though we are having problems, and we can tell you where it might be wrong from the initial set-up to the conclusions. We have valuable information to share. We must be, and we will be involved in each part of the research from the initial set-up of the protocols, to the carrying out, to the interpretation. That is incredibly important. For example, the Ranch Study on Vietnam Veterans on Agent Orange. When you have the Air Force involved and you don't have a vet panel to balance it, you may not have the actual interpretation that you need. And those interpretations do not need to be controlled. We need the data. We need a centralized research center that all this data can go through, get out there on the Internet so it's readily available to researchers, and doctors, and to the vets. The vets need it so that they can get support if someone's been diagnosed with a cancer. They need their support group. They could call another individual in their unit that has that problem. There's a connection there – the family connection. The support mechanisms that need to be there. We need that data out on a central website. We need the research project data out so that others, so we can work more effectively and quickly. So, we need a centralized research.

The other thing is that you need to think about accessibility and equality for your vets. The antibiotic study that is started, the test sites, there's none in Colorado. We have to get away from the VA hospital being able to say, "Yeah, we'll participate" or "Yeah, we won't." You've got to think about the vets and accessibility to them and for them.

Mr. Donald Edwards

Thanks Denise. Yes ma'am?

Ms. Debbie Judd

I just want to emphasize the data availability. When you go to do your research, if you do not have certain documents, maybe they're classified, then you can't do a complete research, and you can't know what data is out there. This is another reason why you need Gulf War veterans review panels to help you in your research so that we can all put our heads together and find what we can find. If classified data or unclassified data is not made available, and it's not distributed widely, how can we do a complete research and assessment of what we're trying to find out?

I have so many questions when I read so many reports. And there are so many reports I've read and I've thought, well, "This is not in line with what I know." And this is why we need distribution. We need data available. And you need Gulf War veterans giving you some guidance and feedback on what we know. For example, projections of what the outcome of war was. In

the 17 years in the military service that I did, one of my jobs was war planning. Now, it was known what to expect. And yes, it's classified. So, I can't just talk freely here, but we do need the availability of data so that you can know what was expected. I know what was expected. And that's why I can sit here and wonder, "Why is there any wondering?"

Another matter, and it's a small matter, but not so small when you look at it. In 1985 when I had a baby in the military, a record was made up separate from my normal military medical records. I had no idea why, I just thought they did things that way. And when I had the baby, the records went off somewhere. They are not kept in my normal military medical records. I don't know where they went. I don't know why they were kept separate. I don't know why it's not a part of my whole military record. So that when the VA decides to go back in 1985 and find some somatoform dysfunction in me, in that time frame, they don't know that I had a baby then and I was fired from my job. There is an example of some things you need insight into. Thank you.

Mr. Donald Edwards

Thank you. I think, unfortunately, I'm going to have to call us to closure. I hope that everybody in this room not only was here, but heard. You had a charge from Congressman Sanders, and I know the gentleman reasonably well and I know his expectations. And now you've just heard from the people who all of us work for – the people who are suffering, who represent their comrades. And I hope that their voices will guide you through the next two and half days, and will lead you to come to proposals which will lead to treatment trials, which will lead to treatments, which will help my comrades in arms. I would like to thank the panel very much indeed. Thank you.

The session adjourned.

SESSION II
Possible Health Outcomes of Low Level Chemical Exposures: What Do We Know From the Civilian Literature?

David Schwartz, MD, MPH, Moderator
Professor of Medicine
University of Iowa College of Medicine
Iowa City, Iowa

We'll get started with Dr. Noel Rose.

Noel Rose, MD, PhD
Professor of Pathology and Professor of Molecular Biology
Johns Hopkins University
Baltimore, Maryland

Health Effects of Chemicals on the Immune System

This morning I'd like to discuss with you, on one hand, what the possible effects of various environmental chemicals may be on the immune system, and then discuss the methods and the tools that the immunologist has at his disposal to assess these effects – all of this in about 25 minutes. So, we're going to move fairly quickly, but I will, for the more general audience, spend a little more time on this first slide which, as the title indicates, presents the possible immunotoxic effects. That is, the possible effects that environmental agents and more specifically, chemicals, can exert on the immune system.

Now, the immune system, ladies and gentlemen, is the sum total of the composites in the body that provide us with protection, particularly protection against invading pathogenic microorganisms, and to some extent against cancer cells. The essential nature of the immune system is well illustrated by individuals whose immune system has been impaired or crippled. And these days, all of you are familiar with acquired immunodeficiency syndrome, or AIDS as we call it, which is a disease which essentially destroys, in its last steps, the immune system and leaves the patient vulnerable to infection by many different microorganisms and also to the occurrence of certain types of cancers. So the immune system then is always on guard because in the globe in which we live, we are always surrounded by potentially disease producing, potentially pathogenic microorganisms.

So, the first group of effects that can occur following injury of the immune system is a decreased post resistance. In other words, an impairment in the immune response leaving the individual more susceptible to infection and, as I say, to some types of malignancy, some types of cancer.

Now, the immune system has a number of components that we're going to be referring to in the next few minutes. One of the more familiar manifestations of an immune response is the production of antibody, antibody appearing in the blood stream of an individual who has been exposed, for example, to a microorganism, or has received an immunizing vaccine. And that is the product of the B, letter B, cell. The second arm of the immune system, equally important, is mediated not by detectable antibodies in the blood stream but rather by the white blood cells, and particularly a set or a population of white blood cells we call T-lymphocytes. And they are responsible for cell mediated immunity. Cell because it's the T-cell that does the job. And that form of immunity is primarily devoted to protection against microorganisms that are within cells. Antibodies are effective against microorganisms that are still present in the blood, or exposed in

the tissues. But, antibody does not in general reach pathogenic organisms that are within cells. Many of the important viruses, many important bacteria, fungi, parasites inhabit cells. And so we depend on the T-cell mediated immunity. So, some individuals may have impairment of the B-cell arm of the immune system. That is, they will have deficiency in antibody, and they will be susceptible to certain infections, certain types of infections in which the organism primarily inhabits the blood stream or the tissues. So, they are typically people susceptible to pneumonia, meningitis, and so forth. Whereas, patients may have a deficiency of the T-cell mediated arm. That's the cell mediated arm. They will be susceptible to certain viral infections, things like hepatitis or herpes infections, certain fungus infections, pneumocystis, and so forth.

So, we often determine not only that the patient is immunodeficient, but the nature of the immunodeficiency may tell us where, which arm of the immune response is impaired.

Complement is a component of the blood which interacts with the B-cell mediated arm. That is, with antibody, to enhance immunity. And when complement is deficient, we see particular types of infections, particularly a form of meningitis. Finally, the effector of protection in many infections is phagocytosis, and there may be impairment of phagocytosis. And again, these patients have certain pertinent susceptibilities to particular organisms.

So, the most prominent effect of an impaired immune response is an increased susceptibility to infection or an increased susceptibility to certain types of cancers. And I have to present a certain warning here. There was at one time a feeling that immune deficiency leads to cancer in general, leads to increased prevalence of cancer in general. What we've learned is that only certain types of cancers seem to be prevalent in patients with immunodeficiency, particularly cancers of the lymphoid and reticular lymphatic system. So, leukemias and lymphomas and so forth are the ones that we see in patients with immunodeficiency.

The next group of disorders that can result from a toxic effect or an interaction of the immune system with a chemical is hypersensitivity, or allergy in the more common lingo. And there are two major types of hypersensitivity: immediate hypersensitivity which is mediated, again, by an antibody, by a special class of antibodies, and these immediate reactions are the ones that we're familiar with in hay fever, asthma, hives, and they may also give rise to devastating effects of anything injected or anything that gets into the bloodstream such as a animal sting or a bee sting. And cell mediated immunity which most of us recognize as contact hypersensitivity, the sort of rash we get from prolonged contact with something on the skin or certain types of skin tests like the tuberculin skin test. And, again, that is cell mediated very much like the T-cell mediated immunity that I described above.

And then the third possible consequence of an immunotoxic reaction is autoimmunity, and that is the particular area of my own interest, and I hope I'll save a little time to talk about that because it is in some ways the most significant with respect to many of the issues I think that are going to be

coming into this meeting.

So, now I'll proceed a little more rapidly to discuss the ways in which a physician can determine that there is an immunotoxic reaction, with the general theme that this is no longer chaos. When I started in this field, I think there's nothing that engendered more mystification on the part of many of my colleagues than the assessment of the human immune response. Well, time has gone on, we understand a great deal more about immunology, and there are reasonably systematic ways in which one can investigate a patient who may have an impaired immune response. Usually, I'm speaking of immunodeficiency reactions. But, we'll get to hypersensitivity and autoimmunity as time allows. The way in which we do it is to start from the simple and least expensive tests, and yet the most revealing tests, and then go to the more specialized procedures. And I'll go through some of these just to give you a flavor of the kinds of tools that the clinical immunologist has at his disposal.

So, let's look first at the general tests of immunopathology. In all of immunology, one begins with the patient and with clinical signs. I said at the beginning that one of the outstanding properties of the immune system is its reserve. That is, one can destroy or injure a great deal of the whole immune system without there being any important clinical consequences because we have a great reserve in our immune systems. Fortunately, we're born with a highly redundant system, where a defect in one part of the immune system can be replaced by mobilizing another part. That's the good news. The bad news is that that reserve is somewhat limited over the lifetime, and we essentially use it up. For example, we observed that in general older people are more susceptible to infection than younger individuals because their immune reserve has been gradually depleted through the years. Generally, older people are more likely to manifest autoimmunity because they have less control of their immune response. So, the reserve is enormous, but it's not infinite, and it tends to get used up. And one of the dilemmas facing the immunotoxicologist is that agents may have their manifestations delayed because their effect is to hasten the utilization of immunological reserves, you see, as if we encounter a toxic chemical, we may be depleting our immunological reserve, our immunological storehouse, our immunological bank account. And the effects of that may not be apparent for some time. And the effects will also, as we'll see, be determined very much by the genetic inheritance of the individual. So, the effects of a toxic exposure may be delayed in time. They may be very subtle in the way they come about because they will be dependent upon the way in which we consume this bank account, this reserve. And, they may differ quite a bit from person to person. So, I think you see a certain theme emerging here that does make immunotoxicology rather interesting and sometimes rather challenging.

But, we look first for inordinate infection, particularly inability to cope with infection. We look for certain types of tumors when we're looking for hypersensitivity reaction. We look for skin rashes or dermatitis. And, particularly, we look for respiratory disease if we're concerned with allergy. We begin with the simplest laboratory tests, the usual blood counts, and we only get into

the immunologically sophisticated tests when these are indicative of an effect. And I'll go through some of these a little later, but I want to point out that we start with clinical observations. We go through simple standard clinical tests and that almost always gives us the largest amount of information. And, we don't turn to the very sophisticated, and I might say very expensive, until we have some pretty good clue of what we're looking for. That's the way we avoid the chaos that can come with undirected clinical immunological investigation.

So, suppose the clinical and the initial immunopathologic evidence suggests an impairment in the antibody mediated arm of the immune response, which we call humoral immunity. We look for things like the levels of immunoglobulin in the serum. We look for restricted clonality. And then we may challenge the cells in vitro to look for their ability to produce the immunoglobulins. We'll look for B-cells and the ability of the patient himself or herself to develop so called natural antibodies, particularly blood group antibodies. And then, the ultimate test, to challenge the patient to see if the patient can respond to a standard immunogen. And, those are the steps that we go through, more or less in order. Depending again on the clinical signs and the tips we get, we may look for complement deficiencies, either classical or alternative pathways, and I'll deal with immune complexes when we talk about hypersensitivity.

On the other hand, if we have the type of infection that I referred to as dependent upon the cell mediated arm, we would begin rather differently. We usually start with delayed hypersensitivity skin test, the cheapest and easiest test, and still, in my opinion, the most revealing test. Only then do we usually turn to the test where we actually quantitate the T-cell response. Those tests use living T-cells. They are expensive, and often difficult to interpret. And, then we go down through the various factors produced by T-cells, and I won't belabor all of them. The number of interleukins goes up almost as I speak, so there are more and more factors we can look for and they give us a certain amount of information. But, I would say we reserve them for the cases where we already have substantial evidence that there is an impaired T-cell response.

I call this non-specific immunity. That is, it's immunity that's mediated neither by T-cells nor B-cells, and natural killer cell activity is important as a sort of initial line of defense against infection or against tumor cells. So we need to look carefully at that in patients who do have infection. I've mentioned phagocytosis previously, and again, those types of tests are done in patients who have the type of infection we associate with an impaired phagocytic reaction.

Now, I next come to immediate hypersensitivity reactions. Those are the ones that are mediated by a special class of antibody which we call IgE so that we usually look at IgE specific reactions using a test called the RAST test. And then we can look at various cellular manifestations of that release of some of the mediators of allergic reactions, and if we are really concerned with it, and this would be these days practically never, we could actually do a passive transfer test and see if we could transfer the allergy from one person to another.

Delayed hypersensitivity. This is what it looks like. This is someone who is allergic to the metal in a thimble, and you see the contact dermatitis there. It's, as I've said, more difficult to measure. This a typical test induced by a sensitizing agent, DNCB, we apply to the skin to see if the patient develops this typical rash. And that's the easiest test. Or we can do a laboratory test, a lymphocyte stimulation test. These are resting T-cells, these are T-cells that have been exposed to their antigen. They begin to get big and they divide, and we can measure that. But, again, we wouldn't do that unless we have pretty good initial evidence.

Now, finally, I'd like to deal briefly with the topic of autoimmune disease, because I think this is a topic of increasing importance with respect to environmental exposures. How would we know if we're dealing with an autoimmune disease? Well, it's doable. It's not easy, but it's doable. And I think that's the message I'd like to leave you with. And there are reasonably good ways in which we can go about it. And it always starts with the demonstration of autoantibodies, that is, antibodies to self, autoimmune disease is caused by a misdirected immune reaction. Or, and this becomes a little more difficult, to self-reactive T-cells. And we proceed then to using the antibody or the T-cell to identify what the antigen is that induces the reaction, and then develop some sort of evidence that that is actually responsible for disease because the problem is not demonstrating the autoantibodies, that's pretty easy. We can even demonstrate auto-reactive T-cells, it's a little more difficult, but it's doable. The problem is knowing whether those are the cause of the disease or the result of the disease.

Well, just a word about autoimmune disease. Autoimmune disease, and there are a number of these, is due to a congruence of a number of genetic factors. On this slide, they are divided into MHC related factors and non-MHC related factors. MHC are the major histocompatibility antigens, some of the markers we use very commonly in clinical immunology. HLA many of you would be familiar with. It turns out that if we look at all patients who have developed an autoimmune disease, about half the risk, or a little less than have the risk is inherited. And of the amount that's inherited, about half is MHC related and half is non-MHC related. And, we have very good tools for measuring MHC. So, we can identify people who are at greater risk of developing autoimmune disease. The other half is something in the environment, and in all of the human autoimmune diseases, it takes something else. And this is infection in some cases, it's a drug in some cases, but in many instances we don't know exactly what the agent is, but we do know that autoimmune disease only occurs in 50 percent or less in identical twins, so we have to assume that the other 50 percent is something environmental.

Now, how do we know that a disease is autoimmune? Well, there are three levels of evidence. There's direct evidences, indirect evidence, and circumstantial evidence. Direct evidence is wonderful when we get it. It means that we can reproduce the disease by taking antibody or serum from the patient and giving it to another person or an animal and reproduce the disease. Or nature does it for us through maternal fetal transfer, or sometimes we can reproduce the manifestations of disease such as a hemolytic anemia by showing that it occurs in the test tube. In

some instances we can use cell transfer to either nude mice or skinned mice, but unfortunately that's not so easy to do. So, if it's an antibody mediated autoimmune disease, and that's about half of the autoimmune diseases, we can usually be pretty sure it's autoimmune.

If it's cell mediated, there are 3 ways in which we can go about showing a disease is autoimmune. We can take the same antigen, the equivalent antigen, and immunize an animal and show that the disease is reproduced in that animal. We get the same disease. Or, we can look for animals that develop the same disease spontaneously for genetic reasons and then go back and show that it's an autoimmune disease. So, you work either forward or backward. But, the bottom line is you develop an animal model. These days, we have one further step and that is we can genetically engineer animals so they produce the autoimmune disease. So, we're a little more adept at this than we were a few years ago.

Then finally, we're often left with neither of these levels of evidence and we have to go on what I call circumstantial evidence, which are patients with autoantibodies, they respond to immunosuppression, the diseases cluster with other autoimmune diseases, and they are related to HLA, because you'll remember I said the major histocompatibility locus is the one family of genes we know is always involved.

So, to put this all together in one final slide that I'd like to leave you with, this is the way diseases occur. Diseases occur because we have an agent that is responsible for the disease. It may be an infectious agent. It may be a chemical agent. A host who is susceptible to the disease. But the third part of this, and the part that I think is probably going to entertain us for the next day and a half, is the role of the environment because it is really changing environments that is the major feature that causes new diseases, unfamiliar diseases, to occur. Thank you.

Dr. David Schwartz, Moderator

Thank you Dr. Rose. We're going to hold questions until the discussion portion of this session just to keep us on time here. Our next speaker is Dr. Peter Spencer. Dr. Spencer is a neurotoxicologist from Oregon Health Sciences University. He is a professor of neurology and director and founder of the Center for Research on Occupational and Environmental Toxicology. He is the recipient of numerous scientific awards for his novel observations in neurotoxicology. The title of his talk is Health Effects of Chemicals on the Nervous System. Dr. Spencer.

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Health Effects of Chemicals on the Nervous System

Drue Barrett asked me to give a general talk, and I'd like to thank her for the invitation. It will be a very superficial coverage of the subject of neurotoxicity because of the time restrictions.

Neurotoxicity is a direct or indirect effect of chemicals that disrupt nervous system function. Literally hundreds of chemicals are recognized as having systemic neurotoxic potential, and I underline the word **potential**, among humans. Some act directly on neural components, others interfere with metabolic processes on which the nervous system is especially dependent. The neurotoxic properties of chemicals find their expression in the deleterious alteration of nervous system function in the presence or absence of any visible structural damage. Perturbations may appear and disappear rapidly, or they may evolve slowly over days or weeks, and regress over months or years. Neurotoxic disorders may leave scars or may disappear without a trace. If I could have the first slide.

Chemicals that disrupt the mammalian nervous system may be either synthetic substances or natural products of the latter. There are the noxious products of bacteria such as diphtheria toxin, of algae, of fungi, of plants and of numerous phyla among the animal species. Among the animal kingdom I should say. Now these naturally occurring substances usually exhibit very great target specificity, very high toxic potency. Despite the fact that they are natural, they often have very high toxic potency. They have discrete biological actions, and in fact, they are among the best understood mechanistically.

Many other less potent naturally occurring substances exhibit neurotoxic effects when encountered in large concentrations for sufficient periods of time. For example, a number of metals including arsenic, manganese, mercury, (not uranium, we know very little about the action of uranium on the nervous system), a number of other compounds which may be in the liquid state such as methanol, or gaseous states such as carbon monoxide or ethylene oxide may, after repeated exposures, result in neurological change. Even some physiological substances when taken in excess, such as vitamin B6 or exposure to manganese or selenium, can cause quite marked neurotoxicity, in some cases with actual neurological damage.

Synthetic chemicals with neurotoxic chemicals are, in fact, in clinical practice in North America most commonly encountered in association with the side effects of therapeutic drugs. One may also find neurotoxicity on rare occasions in association with over-the-counter pharmaceutical products, with domestic materials, workplace chemicals, pest control agents, a variety of environmental pollutants on occasion, and of course substances voluntarily used to induce euphoria in association with drug abuse. Other chemicals are more exotic in their application, for example, CW agents in relationship to civilian or military settings.

In addition to these settings, I want to emphasize that neurotoxic substances can turn up in some

funny spots. For example, this animal had a widely used and approved fragrance raw material also used as a food additive rubbed on its back for a long period of time. It first became irritable, and then it developed an abnormal posture, and then it became weak. And when we opened the brain, it was clearly quite a marked effect of the colorless agent that had been rubbed on the skin. In fact, the brain was bright blue when we opened it up. We know a couple of aromatic solvents which will do this, organic solvents, but the effect is quite discrete and limited to a very few compounds.

Now the nervous system's vulnerability to chemical attack depends heavily on its developmental state, and I really don't have time to address the nervous system and development, but let me say that, in that setting, it is not only the specific chemical and the dose, but it is also the timing of exposure to the developing fetus that is so critical in dictating the nature, or the presence or absence and the nature of the neurotoxic effect. With regard to the mature brain, there may be, as I indicated before, effects that are direct on nervous system components or they may act indirectly by targeting and damaging, for example, blood hemopoietic system, or liver, or kidneys, or lungs with secondary effects on neurological function.

There are many factors both extrinsic to the nervous system and intrinsic to the nervous system which dictate the presence, the type, and the severity of the effects of a variety of xenobiotics or foreign compounds on the central and peripheral nervous system. If we look at some of the extraneural factors, just consider the issue of exposure because this is so terribly important in relationship with the Gulf War setting. These concepts of exposure and dose are separate concepts, and it's important we keep these in mind. There is only an exposure if the exposure pathway is completed between the release of the substance, the movement across the medium, and the contact with the individual subject. The dose is that amount of material which is absorbed or otherwise taken in by the subject. If the exposure pathway has not been completed, there is obviously no exposure. There is no dosage.

Having said that, among the chemicals which have neurotoxic potential, we think of a threshold of exposure being required for an effect to occur. And, indeed, we are all exposed to chemicals with neurotoxic potential, but the amount and duration of exposure and the dosage that we take in is insufficient to produce an effect. Everybody in this room was exposed to that fragrance raw material that I showed the effects on the animal in the preceding slide. But I would challenge you to find a specific defect.

Among the key factors which influence the dose of an exogenous chemical, the retention time and the concentration of the agent in the body, the substance access to the nervous system (which I'll come to momentarily), the nature of the chemical that actually reaches the neural targets all determine the nature of the neurological response, if any.

Now, with regard to the metabolic fate of a chemical once it's absorbed in the body, this is of

critical importance because, of course, liver metabolism is normally involved in detoxifying chemicals, usually making them more water soluble so that they can be readily excreted. On occasion, as with a certain organic solvent, n-hexane, the metabolic capacity of the body, in fact, generates the proximate neurotoxin, in that case 2, 5-hexandion. So, in fact, the organic solvent has little, if any, chronic neurotoxic potential, but its metabolite is, in fact, has considerably increased and specific neurotoxic potency.

Genetic polymorphisms may be important in modifying or even allowing an effect to appear. Genetic polymorphisms often impact the biotransformation capacity of the body. And use of genetically pure strains of animals in the laboratory may obscure this important real world situation for human subjects. A classic example is the autosomal dominant rapid acetylation trait which is more common among Orientals than Caucasians, which allow the Caucasians to be more susceptible and therefore at greater risk to certain agents such as the anti-tuberculosis drug, isoniazid, to produce side effects, in that particular case, seizures or peripheral neuropathy. The difference is, the genetic difference is in the way in which the body metabolizes that chemical provides a susceptibility to certain individuals that other individuals don't have. Another example might be in relationship to a material which saps up or sponges a potentially noxious chemical that enters the body. The liver and serum enzyme butyryl cholinesterase is thought to have differential expressions in individuals according to their genotype, and individuals who may have certain polymorphisms in this regard may have a smaller sponge to sap up carbamate drugs, or nerve agents, or organophosphates, and thus may be potentially more exposed, that is, the brain may be potentially more exposed to these noxious materials.

Gender may be important in relationship to the neurotoxic response in regard to DEET, for example. It's been hypothesized that female carriers of ornithine carbaryl transferase deficiency have greatly increased susceptibilities to the seizuregenic effects of DEET which are exceedingly rare.

Aging, as in immunotoxicity, is thought to be an important component. Certainly, in relationship to the body's diminished ability to metabolize drugs and to excrete them, this is an important component of potential increased susceptibility to any chemical compound. Beyond that, regions of the brain and regions of the peripheral nervous system undergo changes with the passage of time. Certain regions of the brain, such as the basal ganglia, undergo changes with the progress of time which results in a decrease in the reserve available. Therefore, potentially or theoretically, an increased susceptibility to agents that specifically target that region of the brain. Agents, for example, that might be associated with Parkinsonism.

Nutritional status is a widely ignored and greatly important factor modulating the human response to toxic chemicals. Witness the fact that 500 million people in this world consume casava, a plant which generates sizable concentrations of cyanide. It is eaten with impunity in most parts of the world, but in the setting of protein-calorie malnutrition in Africa, irreversible paralysis results

because the sulfur amino acids required to detoxify the cyanide are present to a minimal degree, and toxicity therefore results.

Co-exposure to other chemicals is an important question. We do have examples of organic solvents which can modulate the effects of specific neurotoxic substances. However, I want to underline something here. Any professional toxicologist will tell you that one substance will modulate the action of a second potentially. That does not necessarily mean one substance will increase the toxicity of a second substance. Methyl ethyl ketone potentiates the neuropathy producing potential of n-hexane. They're both organic solvents. Methyl ethyl ketone cannot produce peripheral neuropathy. Toluene, which has a different effect on the brain among individuals who abusively inhale high concentrations of the material, actually diminishes the neuropathy producing potential of n-hexane when both materials are inhaled concurrently. So don't just think of the simplistic view that exposure to multiple chemicals produces greater effects. It could be the reverse, and of course, once you get beyond 2 chemicals, it becomes immensely difficult to sort out.

Molecular specificity is of overarching importance. The top slide shows you the molecular formula of the fragrance raw material and food additive to which we were all undoubtedly exposed. The bottom compound shows you a closely related compound which not only lacks that blue coloring potential of proteins including brain, it is totally without detectable neurotoxicity. You can see the very subtle change in chemical structure. Such changes can make all the difference in terms of an ability of a compound to have an effect or not to have an effect.

I've spoken of developmental state and access to the neural micro environment. The brain, spinal cord, and peripheral nerves are maintained within a very special and carefully controlled extra set of environment. That environment is separated from the bloodstream by blood brain and blood nerve barriers. But those barriers are imperfect, naturally imperfect. In fact, they're full of holes naturally. Regions of the brain which are required to, if you like, sniff the concentration of certain exogenous chemicals in the blood are normally lacking in a blood brain barrier. Agents such as glutamate given to young animals may produce quite marked destruction of chemicals in certain regions modulating the satiety region in the brain, for example. A classic and widely ignored experiment is that of John Olney who gave glutamate in large concentrations to developing rats and in comparison, or contrast to their litter mates, the young rats grew up fat because they ate more, apparently because their satiety center had been destroyed. The brain, therefore, is protected by a blood brain barrier. Pyridostigmine does not cross it. Bromide does. But the point I want to make is that there are normal regions of the brain which are functionally required to be leaky in order for the maintenance of normal homeostasis. Ditto in the peripheral nervous system. The dorsal ganglia, and autonomic ganglia are normally exposed to materials which are circulating in the blood.

Another important component to the vulnerability of the nervous system is the very design of the

nervous system. First of all, unlike most tissues such as the liver or kidney, the nervous system is organized into many specialized regions which have specific functions such as coordination, or balance, or sight, or memory. So, small discrete lesions in any of these regions may have dramatic biological or clinical effects. By contrast, an equivalent lesion in the liver or kidney would have trivial or no detectable clinical effects.

Another important factor is the architecture of the cells themselves. Nerve cells, for example, in the motor system may project very long processes down the spinal cord, connect with nerve cells and communicate with nerve cells electrochemically in the spinal cord, and these nerve cells may have very long processes which innovate muscle. If you are 6' 5" tall as I am, this cell has to maintain an awful lot of cellular cytoplasm for about 70 or 80 years, hopefully longer, which is quite frankly a ridiculous way to organize a secure, safe system. The materials required for cell function are generated in the cell body and they have to be transported along these long processes. The transfer systems are vulnerable to chemical attack. Look at the vast surface area that this one nerve cell has as a consequence simply of its architecture.

The nervous system also has extraordinary requirements, for example, for blood supply. Fully 15% of the cardiac output is used by the brain for the normal maintenance of its function. This means not only that interruptions of blood supply have dramatic effects, but also it means that the brain sees much more, relative to some other organs, of materials which are circulating in the body, and may indeed have a first pass effect by which compounds can enter the brain rapidly.

So, there are design principles and there are functional principles which greatly exaggerate the possibility of the nervous system being vulnerable to a variety of chemical substances. The way in which messages are conveyed along these processes is an electrochemical system. The ways in which messages are conveyed from one nerve cell to a second nerve cell is an electrochemical system as well, and both of these functional properties of the nerve cell are greatly at risk for perturbation from a variety of chemical substances.

Agents which produce a neurotoxic effect usually have their effects evident within seconds to minutes to days to weeks, and occasionally in a couple of months. The latency period will vary as a function of dose. The larger the dose usually the shorter the latency. The duration of the effect will vary depending on the target of the chemical. If it's targeting the electrochemical system of the brain and the nervous system, the effects are likely to be relatively rapidly reversible. If the agent is causing structural breakdown of the nervous system, the effect will be often slower to evolve. It may continue to evolve after the material has been taken away for some days or weeks. And it will surely, slowly regress, and the individual either recover completely or will be left in a state of semi-permanent or permanent deficit.

It is widely believed among neurologists that all chemically induced diseases of the nervous system are self-limiting. Meaning, with the exception that I just mentioned, once you take the

material away from the subject, the disease will either regress or become static. It will not progress. There are very few exceptions to this rule that we know about. One of them, for example, may be in the situation in which there has been massive exposure to carbon monoxide. The individual takes his head out of the gas oven, and appears to regain normality, but several days later undergoes a progressive neurological deterioration. That's because the cell processes which are required to generate that neurodegenerative phenomenon may take some time to evolve. Another example is where you have a chemical which is stored in the body and released. For example, chloroquine, the anti-malarial given to our troops has, it is thought, a lifetime dosage because chloroquine is stored in the melanin, or sequestered in the melanin surrounding the eye and will leech from that source over a period of time. And retinal toxicity may result if that dose threshold is exceeded. And there are other examples.

This individual has a terrible neurotoxic disease from eating sugar cane contaminated with fungus. He has 2 holes in his brain. He has dystonia. It is a permanent, debilitating neurotoxic condition, but it is not progressive as we understand it. This individual has amyotrophic lateral sclerosis. There are only 3 settings in the world, that is all in the Western Pacific, where we believe that there might well be an environmental trigger that might possibly result in a long latency progressive neural degenerative disease. This is an ongoing research topic. It is not a proven fact. But it is an important lead in terms of thinking about the possible role of chemical factors in the genesis of late life, or in this case early life, mid life neurodegenerative disease.

With regard to the sites of action of chemical substances, I talked about the excitable membranes of nerve cells. Nerve cells have a number of important channels which are required to function normally for proper neurological function to occur. Pyrethroids, which were used in the Gulf may interact with sodium channels and maintain them in an open state for a longer period than is normal. And as a result, there is a rapidly reversible, it is believed, neurological effect featured by paraplegia around the mouth and in the extremities. Potassium ion channels are known to be interfered with by, in the Gulf, certain scorpion toxins. Chloride channels can transport bromide ions, and there was the possibility that a very small number, perhaps on the fingers on one hand, number of people in the Gulf developed the adverse affects of bromine from taking pyridostigmine bromide. Bromine was once upon a time, in the United States, a major cause of illness and large numbers of patients would have turned up at Hopkins in the psychiatry department from taking the sedative bromide. It does have potential dermatotoxic and urotoxic effects. It's not the most obvious ion to put in association with pyridostigmine, especially since the bromide ion is a sedative.

Calcium ion channels are regularly impacted by a number of compounds, and calcium channel blockers such as anti-hypertensives. Very briefly, the neuromuscular junction, and as an example of a nerve effector interface, is an area of very great vulnerability because this is where neurotransmitters may be released. They must be released in packets, they must move across the extracellular space, they must associate with receptors, and there must be a specific response such

as the contraction of muscle. Any number of agents may interfere with the synthesis that transport the packaging, the release, the targeting, the reception, and the destruction of somatic transmitters whether it be acetyl choline as exemplified here, or any of a large number of other neurotransmitters that we require for normal function.

With regard to acetylcholine, we know that botulinum toxin may prevent the release of those synaptic versicles, the acetylcholine. This material may prevent the reception of acetylcholine. You can find this sort of material in blue-green algae sold in health food stores. This material here, the transmitter destruction is an extremely important component because you must take away the neurotransmitter if you're going to get the muscle to relax. And so agents such as pyridostigmine bromide, and organophosphates, and sarin can inhibit the enzyme of the neuromuscular junction and elsewhere, which is important for destroying the transmitter, and thus the transmitter stays around for too long and may result in continued firing resulting potentially in muscle damage and actual muscle necrosis with rapid onset weakness, but usually rapid recovery.

I want to finish quickly on agents which produce structural damage of the nervous system. Certainly agents which produce cell degeneration are likely to produce irreversible or poorly reversible lesions. But, there are other materials, in fact they're more common as far as we understand in the environment, which produce largely reversible lesions. The first one I will show you is a situation in which there is loss of the covering of the nerve fiber axon. This covering, or myelin sheath, should look like this, and it's required for the normal conduction of impulses along the nerve fiber. Certain chemicals are able to target this myelin sheath. It comes off as you can see here, but later on it's put back on again. And so that's a largely reversible lesion, albeit relatively slowly. In cross-section, you can see how certain cells are stripping away the myelin sheath, leaving the axon intact, but you can see the repair process of re-myelination is also occurring even during the period of intoxication.

Other agents such as certain solvents may produce axonal degeneration and leave the myelin sheath, the blue material, intact. And a common pattern here is that the long and large nerve fibers in the peripheral nervous system and in the central nervous system will undergo degeneration of these long axons in the distal region. Many, many compounds, many conditions produce this type of distal axonal degeneration. The one that is most of interest today would be the organophosphate induced delayed distal axonal degeneration producing a pattern of peripheral neuropathy. Notice that although we call it "peripheral neuropathy" the very same axonal degeneration is occurring in long and large tracts in the spinal cord, and after recovery from organophosphate neuropathy, if it has been sufficiently severe, this will recover, but this will not, and the individual may be left permanently with a degree of spasticity as a result of failure to recover from the central nervous system disease.

I need to leave it here, but I do want to mention that in order to make an association between the presence of a chemical agent and a neurological illness, we do need to have the suspected agent

confirmed. We need to have a condition which is commensurate with exposure. We know very little about long latency disease, and I emphasize that it is only an hypothesis that such diseases do exist at the present time in relationship to neurotoxic chemicals. We are looking for consistent clinical patterns. We don't expect that one individual will respond radically different clinically from a second individual that has been exposed for a similar length of time for a similar dosage of the same chemical. The condition generally is self-limiting. And, in order to be convinced about this, we need to be able to reproduce the condition in a reasonable animal model in order to be certain that there is a cause-effect relationship. I'll stop there, and thank you very much.

Dr. David Schwartz, Moderator

Dr. Spencer, thank you for your talk on immunotoxicology. The next speaker for this morning is Dr. Stuart Brooks who is a friend and colleague of mine. Dr. Brooks is internationally recognized for his expertise in occupational and environmental lung disease. Dr. Brooks is a Professor in both the College of Medicine and the College of Public Health at the University of South Florida. He previously served as Chairmen of the Department of Environmental and Occupational Health

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Health Effects of Chemicals on the Pulmonary/Respiratory System

I am a veteran of the Vietnam era, and I want to thank the VA Hospital's Dr. Robert Roswell, Director VISN 8, and Veteran's Hospital at the Bay Pine and the James Haley VA for allowing me really to learn and understand some of the things that are happening in this important era.

I'm going to be talking about the area of pulmonary health effects. What I'd like to do is give you an overview of the pulmonary anatomy structure and function. I'd like to review a little bit about how the lung defends against insults, make the point about what happens with high level exposures so we can understand how the body reacts to various chemicals, and then talk a little bit about what is known about pulmonary response to moderate or low level exposures. As part of that, just mentioning that it's important to be aware of certain processes that may simulate a respiratory condition, and I want to emphasize particularly that susceptibility, some preexisting or some host susceptibility may be important in the development of many of these illnesses. And also how the body responds is important in the development of these outcomes.

So, let's talk a little bit about some basic information as it relates to structure and function. And what I'd like to do first of all is mention that when we talk about the lungs we also have to speak about the airways, we're talking about the sinuses, the olfactory area, particularly the nasal passages, the vocal cords, the larynx. These are some of the major important locations in the respiratory tract in the upper airways. This is a cross-section of the vocal cords looking at it within the little circle area. And we're talking about that because sometimes the involvement of the vocal cords may actually simulate a condition. This is actually a bronchoscopic laryngoscopic look at the vocal cords that are open. And you can see that there are both of the vocal cords, which are the outer parts where the arrows are. And these may be important in certain conditions that may simulate asthma or simulate respiratory conditions. We also note that there is an immunologic response in the upper airways. There's a variety of factors, but here's an example of the tonsils. These are actually very large tonsils.

Now, when someone has problems with their upper airways, there are a variety of different symptoms or conditions, including postnasal drainage and cough, runny nose and polyps, there may be reflux of gastric contents up into the upper airways affecting the vocal cords, producing hoarseness. There may be, because of upper airway, and sinus and nasal conditions, actually what appears to be upper airway obstruction. There may be aspiration of contents of the mouth out into the lungs. There may be an actual allergic reaction, an anaphylaxis. And then, there may be tumors. Now, this is just a photograph of what someone with a very large, swollen uvula in the upper airways. You can see that it's almost obstructed there.

I want to talk a little bit about the heart and lungs. When we talk about the heart and lungs, we're talking both about the tracheal/bronchi tree which conducts air to the respiratory portion of the lungs where oxygen and carbon dioxide are exchanged. If we look at the trachea and the bronchi, it is a tree-like structure with many generations, perhaps 17 to 20 generations, each one getting smaller as it goes out in the periphery, similar to the branches on a tree. The final outcome being the leaves, or the respiratory unit in the lungs. Now, if we look at it microscopically, and it's important because we can help understand what is happening biochemically and microscopically. We have the lining of the respiratory tract, the epithelium. It's also interesting to see that there are various glands that secrete. There's cartilage. And then, particularly in the case of asthma, there are smooth muscles which can contract and can produce acute and chronic changes.

The normal lining of the airways, the bronchial epithelium, are made up of ciliated cells, some mucus secreting cells, but we now know that these cells are important and may be the first line of defense. These cells are capable, that is the cells in the tracheal/bronchi tree, are capable of responding to a variety of insults and producing a variety of responses both chemical and sometimes immunologic, but chemical responses, that may be important at least in initiating some of the pulmonary responses that we see. This is a picture of a cross-cut surface of a normal lung, and when we look down into the respiratory portion of the lung, we see the small airways, the tracheal/bronchial tree, the respiratory bronchi, the alveolar ducts, the various alveolar sacs, the

area where we have alveolar tissue. And if we look at the alveolar tissue, we see it as a very thin membrane where gas exchange occurs. I think it's helpful to look at the airways, and this is an electron microscope photograph showing the various compartments of the alveolar capillary membrane where oxygen and carbon dioxides are exchanged. Here we see a blood vessel. There are two major types of cells. The Type 1 cell, a very flat cell. This is where the oxygen would come across into the capillaries binding with hemoglobin, and also, I want you to be aware that this space on the other side is the interstitial space. In the interstitial space there may be tissues, collagen fibers or other elastic fibers that may be important and stimulated in the production of disease. A second type of important cell is what's called the alveolar Type 2 cell. This is a cell that synthesizes and releases surfactant which allows the lungs to remain open during low lung volumes. That is, it helps keep the lungs from collapsing.

Now, if we talk about the lungs, there are many, many different types of cells in the lungs. And this slide just lists some of those. Some of these cells, like the ciliated cell I talked about, some of them produce secretions, some of them are involved in the immunological response, some of them are involved in the response to injury, there are some neural endocrine cells, there are 30 to 40 different types of cells located in the lungs. Probably one of the most important cells is the alveolar macrophage. This is an electron microscope photograph of an alveolar macrophage which is a phagocytic type cell, that is, a cell that is capable of engulfing particles or materials that may be residing in the lung, and therefore is important in defense. Here, for example, are carbon particles and the alveolar macrophage engulfing these carbon particles. Close by it is a Type I epithelial.

Now, in addition to the Type I, Type II, there's also a large number of immunological cells. This is, again, a photo micrograph of a plasma cell that's present in the lung. Now, how do particles get into the lung? It depends on how big the particle is. So that, for example, if it's a large particle greater than 10 microns, it gets stuck in the upper airways. If it's between 3 and 10 microns, it gets down into the bronchi. It's only the particles that are less than 5 and 3 microns, between .5 and 3 microns, that get down into the very small respiratory units of the lungs. So, when you have pneumoconiosis, or dust diseases, these very smallest particles are the ones that produce a reaction in the respiratory portion of the lungs.

Now, we talk about what types of responses we can have to chemicals. This is really kind of a simple classification, but when we talk about the upper airways, we can get either irritation or obstruction. In the tracheal/bronchial tree we can get asthma, bronchitis, or bronchiolitis. And then into the parenchyma, the respiratory portion, we can get what's called diffuse alveolar damage, which I'll talk a little bit about. Generally this results from a higher level exposure. We can get pneumonia as it relates to either a chemical or infectious origin, or an immunological response. We can get scarring, for example, asbestosis. And we can also get cancer.

So, how does the lung protect itself against chemical and other types of injury. Well, there are

two major defense mechanisms. One in the airways, the tracheal/bronchial defense. And this is primarily produced by these ciliated cells. We have cilia at the surfaces, beating on this carpet of soluble and gel-type secretions. Particles that get onto the escalator are being beat up toward the mouth. There's also macrophages on the surface that can engulf these particles. And then we have immunological lymphocytes, we have glands, we have nerve endings, we have other types of cells that are important in the defense in the tracheal/bronchial tree. The reason I'm focusing on this is because how the individual's defense mechanisms react or respond many times result in disease being formed. So, many times it's the body's own response to an offending agent that produces the pathological and biochemical changes. And when we talk about the alveolar area, the respiratory unit, we have primarily alveolar macrophages, but there are lymphocytes, the ability of inflammatory cells to get into the alveolar ducts and disrupt a variety of things. These cells are important in producing disease.

So, we talk about how does a lung get injured? There are several different ways, and I'm just going to mention them. There can be direct toxicity to the cell by a chemical for example oxidant gases or phosgene gas would be an example where it directly kills the cell or damages the cell. There can be an inflammatory response in cells accumulating, and those cells emit enzymes that are capable of damaging the lungs – these proteolytic enzymes. These cells, when they're activated, these inflammatory cells, cells normally present in the body, can generate radicals of oxygen and other types of free radicals that can cause injury to the surrounding tissue. For example, hyperoxia, that is, high levels of oxygen, paraquat, some drugs, or herbicide. You can have the presence of some inflammatory mediators in part of the inflammatory response that can produce changes. Infection itself can produce changes. There can be lack of blood flow or decreased blood flow like you see in lung transplant. There can be various charged proteins, charged particles such as asthma. There can be obstruction such as pulmonary vascular disease, or there can be an immunological response itself.

So, let's talk a little bit about the cellular related type of injury. A major factor in producing injury to the respiratory unit is by the polymorphnuclear leukocyte or the neutrophil. This is a photo micrograph electron microscope of this cell. And basically, what the cell does is that it becomes activated and it can produce injury because of either some of its products that it produces whether it be the enzymes, whether it be the oxygen radicals, but we also know that there are other types of processes that result from cells, tumor necrosis factor, a variety of other cytokines, complexes from inflammation, immune complexes, certain chemicals produced by cells, mediators that are part of an inflammatory response, leukotrienes, prostaglandin, processes that damage surfactant which is normally present in the lung and leads to collapse. These are all things that are part of the cell response that causes injury. And the body has, as defense mechanisms, processes such as antioxidants, antiproteases, scavengers for some of theses processes, and ability to metabolize and degrade these chemicals.

The alveolar macrophage is important, for example, in producing scarring in the lung. We now

know that the major reason for developing scarring in asbestosis and other types of pulmonary fibrosis is that there are recruitment and proliferation of a number of alveolar macrophages which put out a variety of cytokines, chemicals which induce inflammation, and chemicals that are growth factors which recruit and enhance fibrotic tissue to produce the scar reaction.

This slide shows some of the factors that can produce diffuse damage to the respiratory unit. Various drugs, some of them used for treatment of heart disease, for cancer, certain inhalants, gases, oxides and nitrogen, ozone, phosgene, herbicides, x-radiation, and endotoxemia.

Now, depending on the physical and chemical characteristics of the drug, depending on the intensity of the exposure, and importantly, depending on certain host factors which may be the person's own genetic host-defenses or certain pre-existing health status – all of those are important in determining whether or not a person develops a pulmonary condition. Also, the properties of the chemical itself may be determining the site of the injury. So, for example, gases that tend to be soluble are more likely to cause the effects in the upper airways, the upper airways and the upper bronchi. So, chlorine, ammonia, certain aldehydes, sulfur dioxide, certain acids when inhaled, tend to cause more effects in the upper airways because of the properties of that chemical. Likewise, those that are not so soluble are able to get down into the more peripheral airways and alveoli like the oxides of nitrogen, nitrogen dioxide, phosgene and certain other chemicals can actually get down and be distributed in the lungs. And then there are some chemicals that can be inhaled, get into the body, produce perhaps even some neurological effects and produce other effects, but produce little or no injury such as toluene, xylene, carbon monoxide doesn't produce any pulmonary damage but it produces a great deal of central nervous system damage, or it may.

So, let's talk a little bit about high level exposures. The two examples that I'm going to use are diffuse alveolar damage where the respiratory unit's affected, and asthma where the airways are affected. So, let's talk a little bit about diffuse alveolar damage. This is an x-ray of an individual who has what's called *acute respiratory distress syndrome* due to some sort of high level exposure to a chemical gas. And you can see diffuse infiltrates throughout the lungs. The person has had a severe drop in their oxygen concentration, they have a very stiff lung. And if we look at what happens pathologically, we can show that there is actually a very well defined course of pathology in the lungs. Initially there is, within the first few hours, edema, fluid, there is laying down of protein around the walls of the alveoli, then there are inflammatory cells that develop and then finally, there may actually be fibrosis. So, here for example, is an early stage where there is swelling or edema in the lungs. This is the lung tissue. This is normally very thin. Here you can see the swelling in some inflammatory cells. You can see that in the cells, the cells have what's called these hyaline membranes, the edema. This is an acute high level exposure. Later, after several hours or days, there's proliferation of the cells you can see, the beginning of thickening of the interstitium, and finally this is a special stain that shows the scarring of the lung that develops after 2 to 3 weeks – the collagen formation.

If we look at the x-ray, we can see some early changes of scarring, and here is a CT scan (computerized tomography) that you see the scarring occur, mainly in the peripheral parts. Sometimes, it's very small airways, the terminal airways that are affected, bronchiolitis obliterans which this is an example of. Nitrogen dioxide, for example, will do that. The second type is asthma, and asthma is a disease characterized by cough, wheezing, and shortness of breath. There are nocturnal attacks, there is variable airflow limitation which resolves either spontaneously or with treatment such as a bronchodilator. The person has characteristically a twitching airway, that is, they react to various non-specific chemicals, odorants, pharmacologic or physical triggers including cold air. And because of that hyperresponsive airway, the person with asthma is symptomatic and will often respond to these non-specific triggers which may include walking through an aisle where there are detergents, or when someone has a heavy chemical. But this is because the person's airway is hyperresponsive. And if you look at them pathologically, we find that in their airways, there is evidence of inflammation, particularly eosinophilic inflammation. This is a biopsy photomicrograph of someone with asthma where there is intense inflammation in the walls of the airways.

Now, in 1985, my colleagues and I reported on an entity we called reactive airways dysfunction syndrome which was essentially asthma that developed after a high level, brief irritant gas vapor and fume exposure. Following that high level, brief irritant exposure, the person developed asthma for the first time. Allergy did not seem to be a factor in those individuals, but what was characteristic of the exposure was that it was almost always an accident in some confined space. This slide just shows you the breakdown of the 10 patients that were originally described from uranium hexafluorene explosion, to large spills of hydrazine, to a variety of other types of irritant, gas, vapor and fume exposure. But, in each of these situations, there was a high massive level exposure, the exposure was irritant in nature, it was a gas vapor fume (not a dust), it was of such severity that it required immediate health care or hospitalization, the effects were documented within 24 hours with onset of wheezing, shortness of breath, bronchospasm, sometimes reduced oxygen tension. And when evaluated, when I saw these patients months or weeks later, they all required treatment and were treated as an asthmatic.

Subsequently, there's been a number of papers on RADS, reactive airways dysfunction syndrome, and basically to summarize the natural history of RADS, that is, what happens to someone that undergoes or develops asthma due to high level exposure. Well, in most cases, it tends to stabilize, and does not worsen. In many cases, they may have continued non-specific airway hyperresponsiveness for years. In some cases, the asthma resolves and they may continue to have persistent symptoms due to the fact they have non-specific airway hyperresponsiveness. And what I mean by non-specific airway hyperresponsiveness is that they respond as all other asthmatics do to various things such as cold air, sulfur dioxide, smoke, exercise, and a variety of pharmacological and chemical agents.

Now after that, the RADS publication, there were a number of other papers that occurred in the

literature that were RADS. Some of the cases reported irritant exposures, not just briefly or lasting one day, but lasting days and weeks. And there were some reports of asthma developing from low level irritant exposures either called RADS variant or low dose RADS. That is, in this case, asthma could develop after exposures lasting weeks or days presumably from low level exposures. So, the question is, can other types of exposures other than massive, such as low or moderate doses of and irritant exposure, lead to asthma, either initiation or persistence of airway hyperresponsiveness. So as part of that, just showing you some data on another study that was published about a year ago in which we looked at individuals who developed asthma with a low or moderate level exposure to an irritant. And what I want to do is just summarize very briefly some of the criteria and some of the findings, particularly the findings that there seems to be host susceptibility. The criteria was that there was intermittent, repeated, or continuous exposure to an irritant gas vapor or fume over days or weeks. The asthma developed temporally during the time the irritant exposure was ongoing, and the asthma developed during that time. And the odds of an onset and cessation of exposure were not greater than 24 hours. In other words, they had to develop the asthma during the time they were exposed. This is a population, and what I want to do is focus on this top group of 54 patients that had irritant induced asthma, the age distribution, and basically the three groups of adult onset regular asthma that you see in the population, not exposed, the bottom, allergic type asthma, and then this is irritant non-allergic type asthma. I think the point that I want to emphasize is that when you look at this population, there are two things that were present. Either they had a history of asthma in the past that was in remission for years or decades, or that when you look at these individuals, they tend to be atopic. This just shows you the prevalence of atopic. So that this group with irritant induced asthma to a moderate to low level exposure, and this is some of the exposures that they had (similar to that with RADS, but with low or moderate doses). They had development of asthma, but about 30% of them had pre-existing asthma in remission. 70% had pre-existing atopy, that is, they had an allergic diathesis. And from my studies, it appears that they cannot initiate asthma after low or moderate doses unless there is some susceptibility that is pre-existing.

Now, there are other conditions that can simulate, and if I could take maybe a couple, 2 or 3 minutes, in this slide, we list conditions that can simulate or appear to be asthma. And I'm going to briefly just mention some of these because many times patients that I see and patients that have been reported who are exposed to chemicals, develop symptoms, respiratory symptoms, may have these other non-asthma type conditions: vocal cord dysfunction, upper airway disease, misdiagnosis of asthma, non-suspected airway hyperresponsiveness, multiple chemical sensitivities diagnosed as asthma, and hyperventilation syndrome or panic attacks. Now, recently, a few months ago, Dr. Perkner and the group at Denver Jewish reported in the *Journal of Occupational Environmental Medicine* on 11 cases of vocal cord dysfunction where individuals developed a temporal relationship between an irritant exposure, not high level, but moderate to low level over a period of time, and developed vocal cord dysfunction, that is spasm of the vocal cords in response to triggers after these particular exposures. This is an example of a vocal cord that's adducted, that is, it's causing obstruction. The irritant, this is the kinds of exposure that were

reported in that article, and the onset was within just a few hours. There's another paper by Dr. Bucca that was published in *Lancet* a few years ago, and what that says is that non-pulmonary upper airway disorder such as sinusitis, nasal disorders, may actually simulate asthma and cause cough and actually produce other changes that can be confused for asthma.

There is often an over-diagnosis so that Dr. Joyce and his colleagues in *Chest* found that when they looked at patients who came in with a diagnosis of asthma by their primary care physician, in most cases, more than 88% of the times, the diagnosis was not confirmed by a pulmonary specialist. In fact, they did not have asthma, they had been put on medications for almost 3 years, and they were under-diagnosed or poorly diagnosed as having asthma. There is a segment of the population, perhaps 2% to 10% that has non-specific airway hyperresponsiveness.

Finally, we talk about irritant induced asthma, we have to think about an asthma due to chemicals, we have to look at all the other parameters that we talked about – vocal cord dysfunction, multiple chemical sensitivity, and other conditions. So, in conclusion, we have to look at, when we're considering asthma, is it really asthma, was there a massive or low level, if there was, is there a susceptibility, are there other conditions such as upper airways disease or vocal cord dysfunction, how well is the severity documented, and are there types of pre-existing conditions that might make that individual more susceptible? Thank you.

Dr. David Schwartz, Moderator

Thanks very much Dr. Brooks. At this point, I'd like to open up the discussion, so please come to the microphones, ask questions to any one of the panelists, any one of the speakers. Please introduce yourself when you ask a question, and also spell your name and give your organization.

Discussion

Meryl Nass, MD
Freeport, Maine

I'm a physician . . . I'll take this opportunity to ask Dr. Spencer about something we discussed 5 years ago which was an epidemic in Cuba which probably, the putative cause I believe was cyanide in a setting of nutrition deficiency. And it had, that epidemic had some features similar to Gulf War illness in that it affected the central peripheral nervous system, the autonomic nervous system, in some patients caused cognitive and emotional changes. And I wonder if he has any comments about that and how it may relate to the Gulf War illness we're talking about now.

Dr. Peter Spencer

This was the largest outbreak of peripheral neuropathy and visual deficits in modern times that

occurred in Cuba. It began with difficulties in vision in the western part of Cuba which spread eastwardly. And as it spread, it changed to a clinical pattern of both visual deficits and also distal symmetrical, predominately sensory but to some extent motor polyneuropathy. By the Cuban's count, over 40,000 people were affected. The exact etiology is not clear, but it's clinically very similar to a disease which is pronounced "strong" but it's spelled Strachan Syndrome which was originally described in the Caribbean. It was also described among prisoners of war and is also seen in certain settings such as Nigeria where there is, indeed, a high cyanogenic diet. It is apparently a combination of poor nutrition, excess energy demand probably is a feature, and probably exposure to cyanogenic plant material. It rapidly disappeared after times improved, and after vitamin supplementation was provided. It's a disgrace, frankly, that the disease occurred in the first place, and it resulted from a number, or combination of things, that is, the collapse of the Soviet Union, a huge storm – the storm of the century, and possibly the fact that the leader of the country had encouraged everybody to grow cassava which is a cyanogenic plant, although the levels of cyanide in that plant were not particularly elevated. Anyway, it will occur again in a variety of other settings where malnutrition is a dominant feature. It is clearly distinct and different from Gulf War unexplained illness.

Mr. Anthony Hardie

Dr. Brooks, this question is for you. I thought it very interesting you discussing the misdiagnosis of asthma. I'm one of those Gulf War veterans that was misdiagnosed with asthma immediately upon my return from the Gulf. I've had chronic sinus problems since then, have had a couple of surgeries, steroids for the last several years and, so on. I'm curious, the point that you brought up that I found very interesting was your suggesting about an element, once it's removed, that it, as far as what the effects are afterwards, perhaps you could talk about what, I guess what happens after, I guess I'm just curious as far as why the surgeries aren't doing any good. I'm an example of many Gulf War veterans that are having these same sorts of problems, who are having all kinds of surgeries and so on, and things just are not improving.

Dr. David Schwartz, Moderator

Stu, before you answer that question, I'd like you to keep the answers brief. We have a lot of questions. And I'd like each one of the speakers to address that question of the persistence and the worsening of the symptoms, because it came up in each one of your talks. So, maybe we could take just a few minutes for each of the speakers to answer that question.

Dr. Stuart Brooks

Just as far as persistence with sinusitis and things like that, once a process starts, many times when the stimulus that caused it is over, the process continues. So, that's frequent with sinusitis secretions and so forth, and making sure the drainage, and that's why surgery. So, you may have

symptoms afterwards. My point that I was making was that sometimes with an injury, particularly an immunologic injury or other types of injury, you may have continued symptoms and processes because the changes that occur in the cells and the body perpetuates these inflammatory or other changes that may persist for months or years, even after termination. An example would be like the allergic sinusitis where it continues even after surgery and so forth.

Dr. David Schwartz, Moderator

Dr. Rose.

Dr. Noel Rose

Yes, I guess the question that you want us to address, and a difficult question, is how could we explain either persistent effects or effects that occur a long time after the original injury – latency. We're on unfamiliar territory here. The effects that we're used to studying are the immediate effects, and effects that disappear. For example, in drug induced autoimmune disease, the effects usually occur while the drug is taken, and when one withholds the drug, the symptoms disappear. That's what we know. Those are the systems we're used to because there's a time relationship between the cause and the effect, so clearly those come to medical attention. The long range effects are the ones that we need to learn about because they are distant from the cause and, therefore, not associated in our minds with the cause, or even the mind of the patient with the cause. And I'm afraid that there we are very much on uncertain territory. Are there long range effects? Could one be exposed now and have the effects 10 years from now? Well, there's perhaps one thing to go on that might suggest that at least in the realm of an immunologically mediated disease, namely, Type I diabetes. That's a disease which is due to destruction of the pancreatic beta cells. It apparently in most people starts in childhood and I believe that's the case because the male/female ratio is 1:1 in that disease. It's one of the few autoimmune diseases which is not predominantly a female disease. And yet, in many patients, and we're learning more and more about this, the onset is delayed by many years. So, I think it's not inconceivable that there are long range effects.

Dr. David Schwartz, Moderator

Dr. Spencer.

Dr. Peter Spencer

I can probably best answer that in the following way. In 1981, a number of drug addicts in California suddenly developed at a very early age advanced Parkinsonism. This was traced to a contaminant of a designer drug. The contaminant was called methylphenyl tetrahydroperidine. Among the cohort of individuals that was exposed to this material, some were clinically normal.

But, examination of the brain by positron emission tomography using a fluoro- DOPA tag demonstrated that, in fact, the basil ganglia were attenuated in size. If you have an agent which is acting on the part of the brain which, as a consequence of the aging process, is also undergoing diminution, and there sort of happens to be a threshold for that effect to be expressed, you can see how one could have a long latency disease occurring. For example, if I had been the subject and had a slight hit on my basal ganglia, and as I advance with age, my basal ganglia would diminish anyway, I would cross the threshold eventually which is believed to be around about 80% loss. There's great redundancy in the nervous system as well, in parts of it. At that time, suddenly this disease would pop out of nowhere. That's one possible explanation. We suspect that in relationship to the high incidence of ALS and Parkinsonism dementia in 3 Western Pacific loci, that there may be another, as yet to be discovered, biological explanation for what we think is a long latency disease in which an environmental factor, chemical factor, has a prominent role. It's too long to discuss now, though.

Dr. Beatrice Golomb
RAND Corporation
Santa Monica, California

This is directed to Peter Spencer. Thank you for a very nice talk. I just had two comments to complement what you said. On the list of possible effects by toxins on receptor systems, you mentioned receptor activation, but also receptor desensitization and down regulation of potential permanent effects that are known to occur with cholinesterase inhibiting agents.

Dr. Peter Spencer

Thank you very much. Your point is very well taken. One could have spent the next 6 months discussing the potential range of effects on these neurotransmitter systems because it is a site of very great vulnerability of the nervous system. And not only may the effects be expressed during the presence of the toxin as you know, but also the withdrawal from the material may also precipitate a vast number of usually reversible neurological effects. But, on occasion, as in the case of neuroleptic dyskinesia, these effects may be very poorly reversible.

Dr. Beatrice Golomb

Right. And part of that can be because if there's down regulation, and you continue the agent, then that masks the down regulation. The other brief comment was to compliment what you mentioned about bromide and bromism and kind of as a reassurance to the Gulf War veterans, there was a study in which bromide was administered to a set of subjects at 34 times the daily dose that Gulf War veterans received in PB for a period of 12 weeks. The blood level of bromide achieved was 34 mg/dl which is still a bit below the 50 mg/dl that's normally required for diagnosis of bromism. So, at a substantially higher dose of bromide for a longer period of time,

there really was not evidence of bromism. And as you mentioned, only in exceptional circumstances might bromism have been a plausible etiology.

Dr. Peter Spencer

That's right, and I didn't want to make a big deal of this, but the issue with bromism is that if you happen to be dehydrated, remember people were sitting in the Gulf for 6 months, and you happened to be salt deprived, which you were not likely to be salt deprived because of those rations, but if you were, you would have had greatly increased susceptibility to bromide because the residence time of bromide goes from a few hours to several weeks in the setting of dehydration. A 1926 experiment showed that it could be several weeks or even months in a dog administered bromide in the setting of dehydration.

Dr. David Schwartz, Moderator

We only have time for 2 more questioners.

Albert Donnay
Director, MCS Referral & Resources
Baltimore, Maryland

Separately I'm the research coordinator of an MCS immunology study at Johns Hopkins that Dr. Noel Rose is also involved in. Our Principal Investigator is Dr. Joe Marwick. My question is for Dr. Spencer, and I welcome other comments. It concerns your recognition that there are some agents that don't fit the pattern you showed in your last slide, and that carbon monoxide is one of those agents. I may have missed it, but I don't believe you mentioned that carbon monoxide is actually an endogenously produced neurotransmitter. And I wonder, given that CO has so many effects systemically throughout the body in its neurotransmitter function controlling memory, learning, sensation, heart rate, respiratory rate, GI function, blood vessel tone, etc., etc., whether you recognize what has been controversial in medicine for a hundred years, a chronic syndrome that results from a chronic low level CO exposure, like NO without an acute effect, perhaps even recognizable at the initial exposure, but if exposure continues over time, there's a hundred years worth of literature suggesting a pattern of symptoms very similar to this. I'm not suggesting it's the only cause, but I wonder if you could suggest ways we might look at that, and if hemoxygenase, that's the enzyme that produces CO in the body, may be involved since hemoxygenase is one of the main stress proteins that reacts to all the type of stimuli we've been talking about, not just chemical but biological, physical, social, etc.

Dr. Peter Spencer

Well, your first point that NO is a physiological regulator, including of synaptic function, is well

taken. I mean, one might add the possibility that since cyanide and CO are also potential endogenous materials, that neurobiologists might want to look at those as potential endogenous regulators of a variety of functions. With regard to the question of chronic CO toxicity, I think it's a very reasonable question that you raise. I think it has not been ruled out that there might be persistent effects, or chronic effects. It's certainly an area that would be well studied. A priori one might expect that there would be effects on the peripheral nervous system in addition given the transport systems, which are so much required for the shuttling of materials along those long axons, are energy dependent systems. We know of a variety of situations in which exposure to agents which perturb energy regulation are associated with slow axonal demise. This question of peripheral neuropathy among chronic CO exposed people, to my knowledge, was last looked at by Margaret Grunnet about 20 years ago. Maybe it's time to look again.

Gina Whitcomb
Executive Director, Desert Storm Justice Foundation
Guthrie, Oklahoma

My question is for Dr. Spencer. As you were talking about the effects of chemicals on the nervous system, you made the comment that the brain undergoes changes over time. I would like a better definition maybe of what range of time we're talking about. I mean, here we are 8 years after the war, and in Oklahoma we have a high Gulf Veteran population, and in the SPECT scans that are being done, and what we're seeing going on there, and what would be the time range you might want to see about repeating some tests?

Dr. Peter Spencer

Well, mammals and humans seem to undergo deleterious changes as a consequence of the passage of time, and I'm speaking of decades, a half century in this particular situation. If I can phrase it this way, if we live long enough, we'll all probably develop something which looked a little like Parkinsonism. We will all develop, if we live to the age of 70 or 80, deficits in our ability to perceive sensory stimuli in our legs because we will all develop a very, very low grade peripheral neuropathy. But unless you happen to be a concert pianist, you probably won't miss the fact that you cannot detect vibratory stimuli as well as you could when you were 20 years old. So, these can be sub-clinical effects which accrue with time, which can be in addition or can add to the effects potentially of the sub-clinical exposure to a chemical substance, or indeed a clinical exposure to chemical substance. We studied a group of patients who, in the Spanish Civil War, were excessively exposed to the grass pea which is the cause of spastic paraparesis. And we asked the question 50 years later as to whether or not their clinical deficit had regressed, and indeed it had, but to a very, very minor degree quite distinct from the sort of rapid, aggressive, malignant progression that we see in a situation like Parkinson's disease or ALS.

Ms. Gina Whitcomb

Okay, a brief announcement. We have a room that we would invite anyone to come join us at. It's the Fitzgerald room. You can grab lunch, go down, it's a nice quiet setting for networking to kind of get away from the crowd. You just follow the corridor around by the pool, take the stairs down, turn left, and that's the Fitzgerald room. Everyone is invited to come there and have some respite.

Dr. David Schwartz, Moderator

At this point I'd like to let the audience know that they're free to go to lunch. I see that there are a number of individuals that still have questions, and I want to give them the opportunity to ask the questions to the speakers this morning. However, the afternoon session is going to start at 1:30 so if you feel like you want to go grab a bite to eat, please just get up and go out to one of the restaurants and we'll continue to answer the questions for the people at the microphones.

Ruth McGill, MD
San Angelo, Texas

I have a civilian version of neurodegenerative disease mitochondrial encephalomyelopathy. My question is not directed to anyone in particular. It is directed to the room at large and to the planners, the panel at large if you care to respond, and to any future researchers. I congratulate you for having the good sense to leave psychiatry off this panel. We need neurology, immunology, pulmonology, and we need to teach psychiatrists to identify these things better and to follow instructions to help the patients comply with treatment for these things. I would like to suggest as a research idea that we all consider the problem of cellular energetics in all cells. I've noticed that our Gulf War veterans all seem to be prematurely aged, getting back to Dr. Spencer's comment about Parkinson's and peripheral neuropathy and how we're all going to get it eventually. Chronic illness is premature aging and a great deal of chronic illness has to do with failure of cellular energetics. I'd also like for research to be directed at possibly aborting or attenuating this excessively rapid aging rather than a plateau and starting over, let's address nutrition as a possible treatment strategy to, if not improve health, at least obtain stability and stop the downhill skid. Thank you.

Dr. Peter Spencer

If I could just mention that the bad news for Americans, myself included, is that a calorie laden diet appears, at least in animals, to attenuate the lifespan. There's strong evidence that 40% dietary restriction increases the lifespan of rodents, greatly reduces the cancer rate, and among my colleagues in the neurodegenerative field, it is now being suggested that calorie restriction may have something to do with modulating the rate of onset of some experimental neurodegenerative disorders.

Dr. David Schwartz, Moderator

A related topic, which I think was addressed by all three of you is the vulnerable population, and that individuals are vulnerable to different things at different points in terms of their chronologic development, and I think that that's an important aspect to consider when considering why some individuals who went to the Gulf developed disease and other didn't. Can I have the next question?

Dr. William Baumzweiger
Studio City, California

I've been working with Gulf War veterans as a neurologist and psychiatrist and learning immunology as fast as I can for the last 4 years. I want to address not just the energetic problem that Ruth brought up, but also the information processing problem in the central nervous system. I've actually done some studies showing that calcium channel blockers of the dihydropyridine type reduce the cardiac instability in Gulf War veterans. They tend to have a heart rate increase of over 20 beats per minute just by standing up if they're ill. That can be reduced to about 10 beats per minute just by standing up. I assume this is due to autonomic nervous system control over the heart being improved, and we were talking about the calcium channels and how there might be, you know, long term effects on any of these channels. Is there any information on that, or do you have any opinion?

Dr. David Schwartz, Moderator

What you're referring to is the specific beat-to-beat variability of parasympathetic, sympathetic is that right? I don't know that any work is currently being done with Persian Gulf War veterans related to that. Dr. Spencer?

Dr. Peter Spencer

I'm not aware of any specific work, but I would point out that in terms of looking for a potential association, one thinks immediately of the somewhat apparently persistent effects of organophosphates on the autonomic component of the peripheral nervous system. If you go back and look at the Ginger Jake episode in the 1930s when people in this country were poisoned by triethylcresolphosphate, and you look at the follow-up of those individuals 10, 20 years later, a remarkable number of them had residual sensory motor neuropathy. But a remarkable number also had autonomic dysfunction, including cardiac dysfunction.

Dr. William Baumzweiger

Right, that would be brainstem or the pathways to the heart, or the peripheral intubation of the

heart, that's exactly correct. And these are all controlled by calcium channel function as far as I know. That's what I think we're looking at here, because there was not only an improvement in cardiac stability, there was also improvement in 10 our of 17 clinical parameters just using calcium channel blockers alone. We did a factor analysis on this on 80 patients and we found that it held up under factor analysis.

Dr. David Schwartz, Moderator

Next question, please.

Janyce Brown
Flint, Michigan

I'm a mother, I'm a wife, I'm a daughter, I'm a sister, and I'm a friend. I need no other affiliations other than those. I would like to ask the panel why the Veterans Administration and the Department of Defense have not, and will not, truthfully do the diagnostics testings that will verify the natural and endemic cause of what is known as Gulf War syndrome? Those tests being bone marrow biopsy, liver, spleen and lymphatic system tissue aspirates to either verify or eliminate the truthful possibility of the parasitic infection known as viscerotropic leishmania.

My husband is currently dying from viscerotropic leishmania in a hospital in Flint, Michigan. We faithfully over the years followed everything that the Veterans Administration Medical Center in Detroit, Michigan, under the guise of [a doctor there], we followed taking all the psychotropic drugs, all of the full treatment. My husband continued to debilitate and die. After a miscarriage under extremely unusual circumstances, looked much like I had been exposed to mustard gas, specifically asked [that doctor] for genetic testing and counseling. Is there a possibility that this is related to my husband's service being that he was a Military Policeman and Liaison Officer between Allied, Saudi and U.S. Forces, traveled around the area into Iraq, Kuwait, and Saudi Arabia. [The doctor's] response to me personally was, "Just don't get pregnant for 3 months. If you want genetic testing and counseling, you better go find it yourself." Now, this was at the end of 1994. Soon afterwards, *Life's* issue of those children born with no arms, no legs, no eyes, no ears came out. [The doctor] also stated to me verbatim, "You need to stop encouraging your husband's symptoms. He's just going to have to learn to live with it."

I want to know why they continued to circumvent the proper diagnostic treatment to eliminate the possibility of my husband dying from viscerotropic leishmania when they continued to state that my husband needed psychiatric treatment. And as of a letter that I received, and dated October 8th from the Chief of Staff, a [doctor] from the VAMC in Detroit, it said that they had documented, well, our confrontational attitude, and that for my husband to continue to receive medical treatment that had been mandated when vets went to Washington, D.C. in 1930 and were shot down in the street, they weren't going to give my husband medical treatment anymore unless

my husband and I both received psychiatric evaluation and subsequent treatment. Has anyone in here ever heard of that?

Well, I would like to finish, please. No, they're probably not going to answer the question because I already know the answer, and the reason is if it's not written down, it does not exist. If it's not signed, it's not verifiable. And the ultimate verification is autopsy. Yes. There were verified cases of viscerotropic leishmania in Gulf War veterans and you only [have to] cut up so many guys when they all got it to know this is a problem. It's communicable. It has been in the blood distribution of this country for 8 years, and you all know it. And you're allowing it to happen because you're more afraid of the public panic and that I am a national security threat in bringing this information to this conference, you see? You are more afraid of the threat and the panic among the American people, the people of the globe, because it wasn't just American Veterans that got exposed to this. And the people that went over there to serve and protect the American public unwittingly brought this back to their homes, to their families. My husband is dying, my children are both dying.

Dr. David Schwartz, Moderator

I think your time is up.

Mrs. Janyce Brown

No, I don't think so.

Audience

Let her finish. Let her continue.

Drue Barrett, PhD
Chair, Conference Executive Planning Committee
Chief, Veterans' Health Activity Working Group
Division of Environmental Health and Health Effects
National Center for Environmental Health
Centers for Disease Control and Prevention
Atlanta, Georgia

I just don't want this to get out of hand. The panel cannot answer your question.

Mrs. Janyce Brown

No, it's not out of hand. What I'm saying is that we have faithfully followed the directions of the

VA. On June 24th I received a phone call, 2 days after I hooked up a computer to my home, from [someone who] said, "We know you took your husband to the VA in Ann Arbor on the 19th and that blood draw is missing. Actually, we sent it in regular mail to the CDC, and it's missing. Not only do we think that your husband is sick from this parasite, but we think that he has a sub-clinical mutated strain known as viscerotropic leishmania. He didn't know I'd printed off information the night before on someone else's computer that had the incident rate that went all the way back to World War II. 235 per thousand men that were deployed to the Gulf Theater during World War II came down with leishmania, various forms and species.

Dr. David Schwartz, Moderator

We're going to break for lunch.

The session adjourned.

SESSION III
Multiple Chemical Sensitivity (MCS): Research and Clinical Findings Among Gulf War Veterans and Civilian Populations

Moderator Claudia Miller, MD, MS
Associate Professor, Department of Family Practice
Environmental and Occupational Medicine
University of Texas Health Science Center
San Antonio, Texas

We're going to get started. This afternoon there will be 3 sessions. One is concerning research and clinical findings primarily focusing on the Gulf War population. There will be another one focusing on MCS in civilian populations, and a third with patients and physicians who have clinical experiences that they're going to share with us. Each of the speakers will have about 7 minutes with a 1 minute warning before they finish, and any residual time we'll use to ask questions.

The earlier session started getting into the question of how people might have continuing symptoms even after exposures had stopped. And the question of MCS is an interesting one in that it hypothesizes some very specific ways in which that could happen and gives you some civilian data relating to the Gulf War veterans' experience.

I'm going to ask Dr. Bell to start off. Dr. Bell is an Associate Professor of Psychiatry,

Psychology, and Family and Community Medicine at the University of Arizona College of Medicine. She also directs Geriatric Psychiatry at Tucson's VA hospital. Her primary interests are developing and testing a neural sensitization model for multiple chemical sensitivity.

I'm going to keep all of the introductions very short. You have the pink sheets [biosketches] in your handouts, and so to save time, I'm not going to read the very lengthy and impressive resumes of all of the speakers. Dr. Bell.

Research on MCS and Gulf War Veterans

Iris Bell, MD, PhD
Staff Physician, Department of Psychiatry
Tucson Veterans Affairs Medical Center
Tucson, Arizona

Thank you, Claudia. I'm very briefly going to speak about a pilot study we did before we began a much larger scale study we're currently undertaking. Basically what I wanted to emphasize was that we took a random sample of veterans enrolled at the Tucson VA, managed to get a little over 40 of them to answer questions, these were people who were both Persian Gulf and era veterans, got ratings of their global health ratings before the service and then after their Gulf War service, and then divided them into groups depending on whether they felt they'd become chronically ill as a result of their service or that they'd remained healthy. We also had an era veteran group. And just to summarize very briefly what we found, we did observe that 86% of the chronically ill Persian Gulf veterans reported that they considered themselves chemically sensitive. Now, this was a very crude screen. This was not a very elaborate epidemiologic study, but our finding in all the other groups was that 30% of control groups reported the same rate. And what's very interesting and reassuring about that is that is a replication of many different surveys that we have performed in the civilian population in the same area, as well as a replication of what we found in elderly veterans from the World War II and Korean era when we surveyed a somewhat larger group within our primary care service.

We also found that they tended to report multiple exposures, and I'll show you the data very briefly in just a second, so that it was more than one chemical. It was a mixture of substances that they felt they'd been exposed to. They did not emphasize chemical weapons, they emphasized actually more pesticides and insect repellants as being potential factors in their illness. And we also found, as we have in our civilian group, issues with potential familial histories of hypertension and heart disease. We've replicated that finding with several different cohorts in the civilians, and I'll show you very briefly what we have, and comment on some of the issues that we're having now in our work. This is basically the breakdown I just described to you. These are very tiny samples, but they were from a random procedure, and we certainly would hope that we or

someone else would be able to replicate this. This was actually not really a funded study, but more of a pilot examination.

What's also very important to be aware of is that it was multiple exposure. These people have been emphasizing earlier today what we have in our current paradigm of research and a lot of toxicology work, is a much more reductionistic approach, and it is extremely complicated to be dealing with multiple exposures, and yet that is the reality that happened in the Persian Gulf and that happens in the real world. And that seemed to be the actual thing that produced the strongest risk of being one of the members of the ill Persian Gulf cohort. Within the exposures, though, there were particular problems with pesticides and insect repellant as I indicated. Again, we hope this will be replicated in a much larger sample.

These are all people who enrolled at the VA, so we presumably all felt they had some sort of health problem, and obviously, that's again a recruitment bias. But the people who were era veterans who were healthy had the lowest rate of family history of cardiovascular diseases. Certainly what we find is that the Persian Gulf veterans and the era veterans tend to overlap, the ones that are ill. They do tend to overlap in reported chemical sensitivity, although it is slightly higher, even in the Persian Gulf vets as one might expect.

Finally, just to emphasize a point, what was talked about earlier today were primarily issues of what might be a form of neurotoxicity with potentially structural or functional lesions. And I think what's also a very important point to make is that when, I'm a psychiatrist, and when one starts talking about something like somatization disorder, that's simply a label for a collection of symptoms that have no known etiology because psychiatry makes no attempt to put etiology on them. It simply says, "We don't know what they are, but here's a pattern." And we do not know the biology of it, or really the psychology of it, so it's basically a statement. But function is still an important problem, and it's still an important lesion, but more difficult to detect and document.

What we have been focused on in our work is this notion of limbic and mesolimbic sensitization. By that we are not referring to the immune system. We are indicating that there is an entire vast literature within pharmacology, and toxicology, and neuroscience emphasizing the capacity of certain areas in the brain to progressively amplify the responsiveness to environmental factors when the factor is given primarily on an intermittent but repeated basis. I have to emphasize when people are asking about persistent change, sensitization is a process that can become permanent. So when animals are made sensitized in various ways, one can test up to many months, sometimes even a year later, and that's a long time in an animal's lifespan, and it will still be present with no further exposures. And that's what's very important. But this is a process that the Persian Gulf veterans may not be uniquely susceptible to. It's purely and simply something that you would expect to see if someone had exposures on the basis that they did encounter them in the Gulf. And one would expect that one would see it in other groups of veterans as well, and potentially in their families because this process can occur. I'll be speaking about, in a little bit, more in detail

in showing you some of our civilian data during the next section.

I wanted to emphasize here another very important point. People have been saying, "What is ***the*** cause?" And we've been talking about there is no model that could really accommodate all of these different issues. And what I'd like to emphasize here is what's key and important about sensitization is the notion that stress of any type, physical or psychological, endogenous mediators (some that we think may play a role in some of the disorders such as substance P agonists which may play a role in fibromyalgia in the central nervous system, cytokines, various hormones), a large number of drugs, and environmental chemicals (Dr. Sorg is here today and has an animal model using formaldehyde, there are others who have sensitized animals to toluene, there are others who have done some sensitization work using lindane in animals). In other words, the brain which controls behavior, gets sensitized and you get persistent changes in what the individual is capable of. Organophosphates and pesticides are also capable of initiating this kind of process.

So, what we're proposing here is something where it is not a chemical or toxin-specific mechanism, but it is a sensitization process which, in fact, is endogenous to the host, and in which all of these things might actually cross-sensitize for which there is animal evidence. For example, stress can cross-sensitize with drugs. I gather my time is up. Thank you.

Dr. Claudia Miller, Moderator

I realize that this is a very short period of time to be able to present. Dr. Bell will have a little more time in the next section. I'd like to next introduce Dr. Donald Black. Dr. Black is a Professor of Psychiatry at the University of Iowa College of Medicine. His research focus has been on compulsive disorders and on chemical sensitivity. He's published several papers specifically on the topic of multiple chemical sensitivity. Dr. Black.

Donald Black, MD
Professor of Psychiatry
University of Iowa College of Medicine
Iowa City, Iowa

I practice at the University of Iowa Hospitals and Clinics, the largest university-owned teaching hospital in the country. My focus is on the prevalence and risk factors of multiple chemical sensitivity syndrome in a military population. This is the Iowa Study that was referred to earlier this morning. As you can see, there are a large number of co-investigators. Dr. Schwartz who moderated one of this morning's sessions is the primary investigator on this particular project.

Our objective was to assess the prevalence of and risk factors for symptoms suggestive of MCS in a military sample, and I'll describe that to you shortly. There was a population based sample of

Iowa military personnel and we conducted a telephone interview that was cross-sectional in nature, meaning we asked them questions about how they are now, and asked some questions within certain time frames. Subjects were drawn randomly from 4 domains:

- Persian Gulf War active duty
- National Guard reserve
- Non-Persian Gulf War active duty
- Non-Persian Gulf War National Guard/reserve

And these are the substrate that we looked at. Just a few words about our data analysis. I won't go into in depth, but we used the SUDDAN program, alpha established at .05. The estimates that we made are weighted and were dictated by the survey design. If you any questions about this afterwards, I'd be happy to address them.

Now, you may not be able to see this very well, but in order to conduct this study, we developed a set of criteria for the multiple chemical sensitivity syndrome. We did that by consensus among ourselves, and many of the co-investigators have experience with this group of individuals, plus we referred to the literature. But let me just briefly summarize what we required. We required that:

- Routine or normal levels of exposure to chemical agents or substance caused the respondent to feel ill;

- Sensitivity is reported in 2 or more of the following areas, so for example:

    - Smog
    - Air pollution
    - Cigarette smoke
    - Newsprint
    - Carpeting
    - Drapery

- Symptoms are reported from 2 or more of the following categories, these are various organ systems so constitutional symptoms like:

    - Fever
    - Night sweats
    - Rheumatologic conditions
    - Cardiovascular
    - Cognitive

- Symptoms led to a behavioral change in one or more of the following ways:

  - Wearing a mask, gloves, or special clothes
  - Changing ones lifestyle
  - Moving to a new home or location
  - Use of special vitamins, supplements, or diets
  - Use of oxygen, anti-fungals, or neutralizing injections or drops

So, in other words, we wanted evidence that the person was sensitive, that they had symptoms, and that they had altered their behavior in some way. So, this is our definition. This is our starting point.

Now, let me quickly go through the data. Let me first point out this figure here. This is the percentage of all subjects who met our definition for MCS, that's 3.4 percent of this entire military sample of nearly 4,000 individuals. Now, let me direct your attention to this column. These are the individuals who actually met the criteria, 169 persons. And of them, 28.6 percent had been given a diagnosis of MCS by a physician. And these are the agents that they report they're sensitive to. So, for example, 69.4 percent say they're sensitive to copiers, printers, and office machines. Down here, 58.8 percent say they're sensitive to cosmetics, perfumes, and hair spray. Various behavior modifications and treatments, just for example, vitamin supplements and diets, were used by nearly 28 percent of that group. Moved to a new home or location, 25 percent. So, as you can see, all of these symptoms are very common in the MCS group.

Now, let me direct your attention first to this column. These are the individuals who meet criteria for MCS. And we have various psychiatric and physical disorders here that we assessed - 34 percent of the MCS subjects met criteria for major depression, I'm not going to go through all of these, 56 percent met criteria for any type of depression, 19 percent - generalized anxiety disorder, 15 percent - panic disorder, fibromyalgia - 59 percent, chronic fatigue - 6 percent, cognitive dysfunction was very common - 55 percent, respiratory symptoms - 76 percent. So, we see we have an excess amount of physical and psychiatric symptoms in this group of individuals.

This column shows you the odds ratios. In other words, the comparison of the MCS group to those who do not meet criteria, essentially the control group. The only conditions up here that were not excessive in the group of people with MCS were any type of cancer, and then alcohol abuse. I know from my earlier research, Dr. Bell's work and others, that MCS subjects tend not to abuse drugs or alcohol which I think is a highly interesting thing.

Now, we ran a univariate logistic regression. These are the positive, or statistically significant, findings that emerged. These are not all of the findings from the logistic regression. Persian Gulf War deployment odds ratio, 1.9. Just a few others. A physician diagnosis of MCS, the odds ratio was 27.8. Ever seen a professional for mental health reasons, 4.0. These are various psychiatric

conditions with fairly high odds ratios.

And, I'm out of time, but let me just show my conclusions:

- Self-reported symptoms of MCS are relatively frequent;
- They're more common in Persian Gulf veterans than controls;
- The study confirms a link between symptoms of MCS and psychiatric status, including prior professional psychiatric treatment, prior psychotropic drug uses, and current psychiatric illness.

Dr. Claudia Miller, Moderator

Thank you. Our next speaker is Dr. Daniel Clauw. Dr. Clauw is an Associate Professor of Medicine and Orthopedics, and he's also Chief of the Division of Rheumatology, Immunology and Allergy at Georgetown University in Washington, D.C. His interests include the overlaps between fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity in Gulf War illness. Dr. Clauw.

Daniel Clauw, MD
Professor of Medicine and Orthopedics
Chief, Division of Rheumatology, Immunology, and Allergy
Georgetown University
Washington, DC

There's 2 issues that I'd like to briefly talk about today in my 7 minutes. One is some data that we've collected in individuals with Gulf War illness that might give us some ideas about the mechanisms that might be operative for the symptom of chemical sensitivity, and then I'm just going to talk briefly about some ideas with respect to current, future, research projects about perhaps better ways to try to measure chemical sensitivity in individuals.

So, again, I'll first talk about mechanisms using the cohort here. This is preliminary data derived from an ongoing DoD funded study examining the relationship between symptoms and various physiologic parameters in individuals with Gulf War illnesses. We've hypothesized that Gulf War illnesses are very similar in many ways to illnesses such as fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivity that occur in the general population. And what we do is we admit people to the clinical research center at Georgetown with Gulf War illness as well as with some of these other illnesses and run them through a battery of tests that are much more sophisticated with respect to looking at how the central nervous system functions in many ways.

For these analyses for this talk, the self-report of chemical intolerance was the dependent measure because, again, what we're trying to do here is try to determine why individuals might be experiencing chemical sensitivity. The independent measures included other symptoms and complaints, physiologic measures of autonomic function, smooth muscle motility in the esophagus, and peripheral and visceral nociceptation, that is pain sensitivity both in the peripheral parts of the body as well as in the internal organs of the body. And then we also collect a very large number of psychological and psychiatric measures because we know that psychiatric disturbances can influence how people report symptoms.

So, what we did here was first look at correlation coefficients within the cohort of Gulf War illness patients with self-report of chemical intolerance. And, this was just a total number of substances that individuals had sensitivity to. We think it's very difficult in many instances to say "yes" or "no" someone has chemical sensitivity because whether you look at a cohort of individuals with chronic fatigue syndrome, fibromyalgia, or Gulf War illness, what you find is a continuum. You find some people who are somewhat sensitive, some people who are moderately sensitive, and some people who are very sensitive. And so we are looking at all of these as continuous variables. And we looked to determine whether there were relationships, again, with all these other parameters. And when there were positive correlations, these same relationships were examined in our other cohorts (i.e. people with fibromyalgia, people with chronic fatigue syndrome, and in normal individuals).

This slide is very busy, but I'll just start from here. We had a group of 20 individuals with Gulf War illness with whom we have complete data. We eventually will have 40 patients in the study, and we right now have about 25. We have 35 age and gender matched healthy normal individuals. We have 49 individuals with fibromyalgia. In the CFS cohort of 102, we just have self-report questionnaires. They didn't go through this intensive physiologic study.

One of the things that we found is that there is a relationship between pain threshold and these self-report measures of intolerance. And perhaps that's not surprising. We view chemical intolerance as a sensory symptom just as pain is. We found that people who have more pain were more likely to report more of these chemical sensitivities. What you find is that holds true both in Gulf War illness population and in the normals. For those of you who are not familiar with correlation coefficients, numbers that are close to 1 are the most significant, and for biological parameters correlation coefficients in the .3 to .4 range are generally felt to be significant. If you run your sample size up very high, you'll find that correlation coefficients of .1 can be significant, but it's not clear those are biologically significant.

Within the group of fibromyalgia patients, there's not a relationship between pain threshold, and self-report of chemical intolerance because everyone with fibromyalgia has a lot of pain. And so it's, again, not surprising to see that in this group that's defined on the basis of pain, you don't find this relationship. But again, you find somewhat of a relationship between pain sensitivity and

chemical intolerance in all these groups.

These 2 things here are measures of autonomic tone. One is by heart rate variability measures, the ratio of central sympathetic influences, the parasympathetic influences. And again, what we seem to see is that people who have a more active sympathetic nervous system are more likely to have these symptoms of chemical intolerance. And these symptoms are less prominent in the normals or the fibromyalgia group, but they tend to go in the same direction.

This was very striking. Now, the numbers here are small because not everyone wants to get a tube put down their nose and have the pressure measured in their esophagus. But there's a substantial number of persons in all of these groups that are willing to do these types of studies, and they're very illustrative with respect to what you can learn about the physiology of an individual. And what we found is that within the Gulf War group, people, this is a Tensilon challenge. What you do is you give people Tensilon which is edrophonium, a drug that increases, it's very similar to pyridostigmine, it increases cholinergic tone in the body. And what we found when we gave people this is that the esophageal tone changes in response to this. This is a provocative test that's used very commonly in gastroenterology. And that, within all of these groups, there was a strong relationship between the number of millimeters of mercury, that is the tone in the esophagus, and giving them this Tensilon challenge. Again, this suggests that the balance in the autonomic nervous system is somehow not normal in individuals with this spectrum of illness, and that people who have imbalances in their autonomic tone are more likely to complain of and sense intolerance to different types of chemicals.

The other thing we found a relationship to is the total number of fibromyalgia and chronic fatigue symptoms. And again, that's not surprising, we and others have shown that a substantial percentage of people who have either chronic fatigue syndrome or fibromyalgia will have chemical sensitivity as one of the overlapping features.

What we didn't find any relationship at all between, again, these people go through 2 or 3 hours of psychiatric testing. And, in our cohort, we didn't find any relationship at all between either the presence or absence of a psychiatric abnormality as occurs in a structured clinical interview, or continuously distributed variables like a Beck Depression Inventory or Anxiety Inventory, or measures of distress such as a Hassall's Inventory. We didn't find any relationship at all between these psychiatric symptoms and the self-report of chemical intolerance in our cohort.

So, I'll stop there. And I won't talk about the other thing that I was going to talk about. Thank you.

Dr. Claudia Miller, Moderator

Perhaps there will be some more time at the end when we get to questions and answers. The next

speaker is Dr. Nancy Fiedler. Dr. Fiedler is an Associate Professor in the Department of Environmental and Community Medicine at Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey. Her research interests and work have focused on neurobehavioral and psychosocial aspects of multiple chemical sensitivity, and the use of neuropsychological approaches for detection and evaluation of toxic substances. Dr. Fiedler.

Nancy Fiedler, PhD
Associate Professor
Department of Environmental and Community Medicine
UMDNJ – Robert Wood Johnson Medical School
Piscataway, New Jersey

I'm going to just provide an overview of the studies that are going on as a part of our funded Center for Environmental Hazards funded by the Department of Veterans Affairs. This is in East Orange, New Jersey.

First of all, I want to just report some of the information about the epidemiologic survey that is a part of our center looking at chemical sensitivity and chronic fatigue in Persian Gulf veterans with Howard Kipen as the leader of this group. This survey includes questionnaires, current health and symptom reports, medical history, emotional functioning, civilian and war related life events, environmental exposures and demographics.

To give you an overview of the sample size, these are veterans from the Persian Gulf Registry which as you've heard of before, clearly that is a particular kind of group of individuals. Of 1,935 questionnaires sent, 60 percent were returned, and the percentage of cases based on criteria for chronic fatigue syndrome and chemical sensitivity I'll report in a moment. Just so you'll understand, chemical sensitivity was identified by two different methods. First of all simply asking individuals, "Compared to other people do you consider yourself unusually sensitive, Yes or No?" And then in addition, "Have you employed any particular lifestyle changes as a result of your chemical sensitivity such as following a special diet, precautions in home furnishings, wearing particular clothing, having trouble shopping stores?" Which has been talked about a lot today. And these are the criteria that we've used in all of our community surveys and veterans studies on chemical sensitivity.

With regard to the rates, chronic fatigue for the 1994 Chronic Fatigue Symptom Check List, which I will show you in a moment, but I won't go through it right now, those that had endorsed no medical exclusions and do meet the criteria for chronic fatigue according to 1994 symptom criteria, the rate is 15.7 percent. For those people who report being, on the one question, especially sensitive to certain chemicals, the rate is 35.7 percent. However, if you go on to require lifestyle changes as I just showed you, then the rate goes to 13.1 percent for more than 3 lifestyle changes, which is comparable, the 3 lifestyle are what we require in our community

group, and more than 2 lifestyle changes, 32.6 percent. So, it's as the criteria become more stringent, then the numbers go down somewhat.

In terms of our other studies at the Center for Environmental Hazards, we bring veterans in, we do the epidemiologic survey, and then based on that survey and other questionnaires sent out to the community, our focus is on bringing veterans in and doing a complete history and exam to diagnose CFS and/or MCS as well as to bring in healthy matched controls. We do a complete diagnostic interview survey to assess DSM-III-R axis I disorders, psychiatric disorders. We do a complete neuropsychological evaluation with standardized tests of concentration, memory, and executive function among other things, as well as computerized performance based tests. We do an assessment self-report of environmental psychosocial stressors, life events, combat exposures, environmental exposures. And also we have an autonomic reactivity laboratory in which subjects go through a standard stressor procedure and their heart rate, blood pressure, cardiac variability, among other things are measured in response to standard stressors.

I should have showed this before. But anyway, this is the case criteria we are using in our center for all studies in which we diagnose chronic fatigue syndrome, and that is the 1994 criteria of persistent or relaxing chronic fatigue with 4 or more symptoms of the following symptoms that last greater than or equal to 6 months in duration. In addition, we are including subjects who have idiopathic chronic fatigue and the only difference is that they meet all the criteria, except they have less than 4 minor symptoms.

For multiple chemical sensitivity, we are using a criteria also in our clinical studies as well as in the epi survey that the sensitivity, they report a specific time when they did become sensitive and that it results in more than 2 of the following 4 lifestyle changes which you just saw before. They are sensitive to more than one chemical, and they have symptoms in more than one organ system. That is comparable to what we are using in our community studies.

Of the veterans evaluated, and we've actually evaluated more than this now, but when I was preparing this slide, this was the number that I am reporting on, of 206 evaluated, 80 percent came in for a complete work-up as I outlined before of all the clinical descriptive studies. These percentages are slightly off, but I'll just go on. 33 percent were excluded for other medical conditions which could potentially explain their chronic fatigue and/or chemical sensitivity. The important thing I want to point out about here is that about 40 percent who met criteria for CFS and/or MCS, that if you notice, about 66 percent here met criteria for chronic fatigue and another then about, this is approximately 37 percent who had CFS and/or MCS or MCS alone. What we have observed in our center, in spite of active recruitment efforts to get both chemical sensitive and chronic fatigue patients is that there is a significant overlap with those who report chronic fatigue and chemical sensitivity. And these are the healthy controls.

I might add that among those with CFS and/or MCS, which should be on there, about 60 percent

have a comorbid current axis I disorder. So that is a significant factor among the veterans that we've seen.

In terms of environmental exposures, and we note here, and this is simply to point out that of those who have chronic fatigue and/or chemical sensitivity, we note a significantly higher rate of combat exposure with and without comorbid psychiatric disorder, a higher rate of reported negative life stressors since the war (not before or during the war, but since the war), and a higher rate of environmental exposures that they report having occurred in the Gulf for which they became ill from those exposures.

This is the final study that we are in the midst of doing right now. I'll go through it as quickly as I can. This is to test the health effects of a controlled exposure to diesel fumes and a psychologic stressor. This study is an attempt to follow up on what we have learned from our clinical studies. And what we learned first of all is that 41 percent of our veterans with fatiguing illness said that they reported becoming ill in response to chemical exposures, specifically diesel exhaust. So, we used diesel as the controlled chemical exposure. We're also incorporating a psychologic stressor because, as you noted before, psychologic stress is an important factor among the illnesses of veterans. And personality factors as a surrogate for axis I disorders in looking in varying these variables in our study.

This is our controlled environment facility, and I just wanted to show you this. This is a stainless steel chamber or unit in which the airflow, and humidity, and temperature are all controlled. The subject, it's about an 8' x 10' room, it has it's own bathroom facility, and this is a computerized system in which we can measure physiologic parameters as well as computerized neurobehavioral function.

This is the last slide. I'll stop. This is our experimental protocol. And I just want you to know this so that in your thinking about future study designs, I've talked about the moderators and the group factors. We're looking at those with CFS and MCS and healthy controls. We're looking at their response under baseline conditions, and then in 5 ppm diesel fumes, not exhaust. And looking at cognitive performance, symptoms, psychophysiologic responses, and neuroendocrine responses in this study. Thanks.

Dr. Claudia Miller, Moderator

Thank you. You did a good job changing those overheads. There's a saying I love, "Some days you're the bug and some days you're the windshield." The next speaker is going to be Dr. Susan Proctor. Dr. Proctor holds a doctorate in environmental health from Boston University School of Public Health where she is a Research Associate Professor. She's very interested in exposures to neurotoxicants, and the effects of those exposures on health. She is participating in the Boston Environmental Hazards Center funded through the VA. Dr. Proctor.

Susan Proctor, DSc
Associate Professor, School of Public Health, Boston University
Assistant Director, Boston Environmental Hazards Center, Boston VA Medical Center
Boston, Massachusetts

Thank you very much. The focus of my presentation is primarily to describe the assessment criteria that we used in several of our studies at the Boston Environmental Hazard Center, and the rates of chemical sensitivity symptomatology, and presumptive MCS that we found in our Gulf War population that we've been studying.

This is just a list of 3 of the studies that are related studies going on at the Boston Environmental Hazard Center. The first 2 are using similar methodology and criteria for MCS and chemical sensitivity assessment, and the last one, which is data analysis, is still ongoing. It's just a mailed survey of the whole Devens cohort and it's using a different screening criteria. I won't describe that, but if people have questions, I can talk about it. I'm primarily just going to describe the results from the first study.

Just by the way of background, this study examined a group of Gulf deployed veterans and included a stratified random sample of 2 larger cohorts. One is the Devens cohort, which Dr. Swanson referred to this morning, and the other is a cohort of Louisiana Gulf War veterans. We also assessed a comparison group of National Guard troops that were deployed to Germany during the time of the Gulf War. This is a slide just showing the age, education, and gender differences. There was a significant difference in the age. The mean age of our group, the Gulf deployed was younger than the Germany deployed group. And because we over-sampled for women in our stratified random sample of the Gulf deployed, there's a higher percentage of women in the Gulf deployed groups than in the Germany deployed groups.

This is just a quick overview. As part of the study, all the subjects participated in, well most all of them, participated in the semi-structured environmental interview where we asked them questions about environmental exposures in the Gulf, where they were, and what their current health symptoms were at the time of the interview. A rather extensive questionnaire, a neuropsychological test battery, psychological diagnostic interviews for axis I disorders and clinical PTSD assessment. And some psychometric scales, the Brief Symptom Inventory, Mississippi PTSD Scale, Combat Exposure Scale.

This is a description of the assessment criteria that we used based on information that was collected on the questionnaire. We considered that a person with symptomatology of chemical sensitivity would report either greater than 1 out of 4 questions about, positive responses to 1 out of 4 lifestyle changes. These are the same questions that Nancy had. They include wearing particular clothes due to chemical sensitivity. Or, they would report positive response to at least 1 of 4 questions about food or alcohol aversions that happened after the Gulf or became worse

such as feeling ill after meals. Or, they also had a positive response to feeling ill on at least 1 out of 12 common odors that started after their return from the Gulf, and these exposures are listed on the slide. They include new carpeting, insecticides, tobacco smoke, paint thinner, natural gas, perfume or cologne, feeling sick in the detergent aisle, hair spray, drying paint, diesel or gas engine exhaust, gasoline, or chlorinated water.

As part of the environmental interview, veterans were asked to report what their current health symptoms were, and for each one of the symptoms that they reported, they were asked a series of questions such as the frequency of their symptom, the intensity, whether they had lost work, and one of the questions was what triggers their symptom, is there any common trigger or anything, circumstance or situation that triggers it? Following Collins' research criteria for MCS, we considered people to have presumptive MCS based on our interview responses if they reported more than 1 symptom that began after the Gulf War, that involved more than 1 organ system, and that were triggered by low level exposures to chemicals, and that couldn't be explained by any diagnosis or medical information provided on the questionnaire. We included those people with an asthma diagnosis and a psychiatric diagnosis in the diagnosis of presumptive MCS.

These are the unadjusted rates that we found in our sample for chemical sensitivity symptomatology and presumptive MSC. The percentage of chemical sensitivity symptoms on the questionnaire in the Devens and New Orleans group was around 20 percent. In the Germany group it was 2.2 percent. We also had a question on the questionnaire that asked people if they'd ever been diagnosed with MCS, and 2 people out of 162 people from the Devens group said "yes." Zero in the Germany group. The percentage of people that met presumptive MCS on the interview was 2.2 percent or 4 people out of 180, and zero in the Germany group. We also have a category for people that have either chemical sensitivity symptoms on the questionnaire or on the interview, but did not meet presumptive MCS criteria on the interview. That was 19.4 percent in the Devens group, and 2.2 in the Germany. This concludes my talk. I can answer any questions later.

Dr. Claudia Miller, Moderator

All right. It looks like we have 5 minutes or so for some questions. I see some people already at the microphones there. If you could locate one microphone and what I'll do is I'll start in the middle and I'll go across the room here. Yes, first questioner.

Discussion

Dr. Meryl Nass

It seems to me that there is an omission from this whole conference, and that is the role of vaccination and the subsequent development of Gulf War illnesses. The anthrax vaccine, of which

I am most familiar, I just want to point out contained formaldehyde, aluminum, benzethonium chloride, and a number of bacterial products, though no attenuated organism. It so happens that many people who were deployed to Germany were, in fact, vaccinated, so that if this vaccine contributes to Gulf War illness, your control group may be confounded by that. And I think it's something that you folks need to think about controlling when you do your studies. There are also other non-deployed Gulf era vets, many who were vaccinated. I just wanted to make that point.

Dr. Claudia Miller, Moderator

Okay. Thank you. I would appreciate it if people could focus on specific questions for the panel and keep them brief given the number of people who'd like to ask some questions. Yes and no answers are appreciated.

Mr. Albert Donnay

Thank you all for coming forward to present your data for the audience. This is the first time that a lot on MCS studies has ever been presented. I spoke before the meeting with Dr. Black about his data, and you mentioned how, when I spoke with you Dr. Black, that you had a cut-off in your behavioral lifestyle changes of 2 out of the 5. And I wonder if you could comment because it wasn't clear here what cut-off you were using. With that 2 out of 5, you told me that the prevalence was 5.6 in the deployed, 5.6 percent compared to 2.4 percent in the undeployed. Today you presented data showing that it was 3.4 percent, so I wonder if that's set with a different number of criteria. And since those criteria are not directly related to disease, but simply reflect the patient's response to the illness, could you present the data for how many people had all the other criteria without the behavioral changes?

Dr. Donald Black

In response to your last question, I can't because I don't have that data at hand. In answer to your earlier question, you misunderstood what I was saying about the prevalence of MCS in the different groups. The prevalence of MCS in the deployed group was approximately 5.4 whatever number I gave you. And the other figure was in the non-deployed group. The figure I showed today is for the combined group, and it's also weighted, so it's not the exact prevalence of 169 divided by the 4,000 subjects that were interviewed. It's a statistical measure that's weighted taking into account various substrata. But it came out at 3.4 percent, which is fairly consistent with some other epidemiologic figures I've seen for prevalence of MCS type illnesses. For example, Richard Kreutzer in California.

Mr. Albert Donnay

But it masks the very significant 2-fold difference between the deployed and the undeployed if you combine them.

Dr. Donald Black

Well, but I showed that in one of the later slides with the odds ratio of 1.9. It was more common in those who were deployed compared to those who were not deployed.

Dr. Claudia Miller, Moderator

Let's move to another couple of questioners, please. I'm sorry. If you'd like to have a dialogue afterwards I'm sure it sounds like an interesting one.

Dr. Beatrice Golomb

This is directed, I guess at most of the panelists, but particularly Susan Proctor and Donald Black who both mentioned increased prevalence of psychiatric symptoms in their ill Gulf War veterans. And in at least one of the comments, and it was noted that one of the reasons this was investigated was because psychological symptoms can influence reporting. But I think it's important to also emphasize that illness can also influence psychological symptoms, and I just want to be sure that in all of this research that's not being lost.

Dr. Claudia Miller, Moderator

Any comments from the panel on that? No? I think everyone acknowledges that. Next question, please.

Dr. Ruth McGill

I'm a patient with a shortened life expectancy due to neurodegenerative illness. Two questions for each of the panelists if we have the time. Number one, what is your position on whether MCS causes psychiatric illness or psychiatric illnesses causes MCS? Number two, what are the sources of your funding? Thank you.

Dr. Claudia Miller, Moderator

All right. Given the shortness of time, but I think it's fine to ask about funding sources. Maybe people would like to just say briefly what their funding is, and then we could have a couple of volunteers who would particularly like to address this etiology question. Funding first.

Dr. Nancy Fiedler

Department of Veterans Affairs.

Dr. Iris Bell

Department of Veterans Affairs.

Dr. Donald Black

Department of Defense and the Department of Public Health for the State of Iowa.

Dr. Susan Proctor

For the results presented up there, the Department of Veterans Affairs. We have other ongoing CDC and DoD studies.

Dr. Dan Clauw

Department of Defense.

Dr. Claudia Miller, Moderator

All right. Now, would anyone like to address this question of etiology? The chicken and egg question. Volunteers? If not, I'll do it.

Dr. Iris Bell

This is something we've addressed in the MCS debate for many, many years. And my position is that the psychiatric symptoms could be from either direction, but that largely within the MCS community, it is a manifestation of the disease process. And the psychiatric and behavioral symptoms are symptoms of the illness. They are not the cause of the illness. They don't explain the illness.

Dr. Claudia Miller, Moderator

That's fine. We're going to stop here and give time for the next panel to come up. But actually, while they're coming up, if you want to ask one or two more things, that's fine, but let's get that next panel assembled here if we could please. Dr. Bell, Dr. Cone, Graveling, Meggs, Solomon, and White. I've been told there's a great deal of interest in this subject. The choice is to cut people shorter than they're already cut and try to have time for questions and answers. Depending upon what the organizers say, we may try to have additional questions and answers running up until the concurrent workgroup sessions, so if some of you want to stay around during

the break as was done at lunchtime, I think that would be fine. I can tell there are a lot of pressing issues related to this question. The question was, "When was a survey done?" Which survey are you asking? I'm not sure which survey you're talking about. Which panelist? All right. Dr. Fiedler's? Why don't you consult with her. I think she's already gone down below here. There she is, right over there.

All right, our next panel will deal with MCS in civilian populations. Again, in the interest of time I'm going to shorten all of these great CVs. I've already introduced Dr. Bell, so I'm going to let her go ahead.

MCS in Civilian Populations

Dr. Iris Bell

What I'm going to briefly, again, run through, and then there'll be many slides that I can address in detail, are the 8 years of research that we've been doing on MCS where we actually do have data. And I'm talking about the sensitization model, I won't have time to present all of the different studies, but we do have a number of studies now supporting and replicating many of our findings.

As a summary of what our basic findings are, and by the way there are handouts on the tables outside in the hall that will give you some of these summary slides that you can take with you. On many of our surveys, depending on how we ask the question, we're finding a prevalence of chemical intolerance, between 15 and 30 percent, in the general population. This is without requiring behavioral change. If you simply ask, "Are you especially sensitive, or do you consider yourself especially sensitive?" the number is around 30 percent. If you ask, "Do you feel ill from the odor of" and then ask people specific questions and require 3 out of 5 on our particular screening index, being "sometimes" or "more often" in terms the rating, it goes down to roughly 15 percent of the population. But we've replicated this numerous times at this point.

As others have found, we're in the range of 4 to 6 percent when one asks about MCS diagnosis by a physician or uses other kinds of stricter criteria for this diagnosis. But one of the most important points, as was raised in the earlier discussion, the notion is that when we get all these psychological findings in these populations, is this the whole story? I think you have to think much more critically and thoughtfully about that question. Persons with chemical intolerance differ physiologically from depressed people and from sexually abused people who do not have high ratings of chemical intolerance. And we have data to support that. We have papers either published or in press that are available, and can be easily found on MEDLINE.

Persons with chemical intolerance do have increased rates of individual difference factors that

relate to risk for neural sensitization. Persons show increased sensitizability in the laboratory. We've demonstrated this with EEG alpha activity, EEG delta activity, heart rate, and diastolic blood pressure. And these are replicated findings. Persons with chemical intolerance with and without lifestyle changes also differ from each other. I would suggest to you that the behavioral response to being sick is yet again another factor, but it may not be the entire story.

Just to indicate to you in several of our studies, we've asked about medical and family history. The disorders that you see up there, including cyst formation, these are obviously especially women because women are more prone to MCS type symptoms. Ovarian cysts/breast cysts, menstrual disorders, migraine headache, irritable bowl syndrome, food intolerances, sinusitis, rhinitis keep on showing up in our data sets. These people don't endorse everything. They tend to endorse things in these kinds of patterns. One thing that is never done in studies that I've heard about, we're asking about family history. I take that from my geriatric background. What we're getting are family histories of hypertension and heart disease, as I mentioned. In two studies family histories of diabetes. We don't know whether it's Type I or Type II. Rhinitis or other allergies. And substance abuse, and this is extremely important and relevant to the sensitization hypothesis. This is a study showing that people with chemical intolerance and lifestyle change show the largest number of family alcoholism diagnoses compared with people with only chemical intolerance without lifestyle change, or normals. And we've replicated this finding in at least 3 different datasets, although they're smaller samples. What's important here is that sensitization is one of the models for craving in substance abuse, and what I would suggest is that the craving that people with chemical sensitivities have is probably more related to foods than it is to drugs or alcohol, but they may well have inherited a biological predisposition to this problem.

We also found that the people with the highest food craving and food addiction ratings, actually on one of the questions from Dr. Miller's questionnaire, were the people that had an identified chemical initiator for their MCS. And then the other people with chemical sensitivity without a chemical initiator were in between, and the normals were the lowest. So, the food craving study, and we've done this in very large samples with college students with 900 people, and found similar kinds of things.

We've also found that when you compare people with depressed or sexually abused women who do not have chemical intolerance, there is a higher resting EEG alpha activity that we find with eyes closed in the chemically intolerant that have not been seen in the sexually abused or the depressed. And we've replicated this in every study so far. It's our most robust physiologic finding. We've also found different EEG laterality in the front, in terms of alpha activity, which is not the pattern that is seen in depression when we directly compared it. We've also seen different correlations between scale ratings of somatozation and the measure of serum neopterin, which is a non-specific marker really of inflammation or of immune activation. The chemically sensitive have correlations that are robust and significant. The depressed individuals do not.

This is just data to show you that the increased alpha that we see tends to happen more towards the back of the head or the parietal region, especially with the eyes closed. We've also seen that there's more disruptive polysomnographic sleep in the chemically intolerant, there's poor performance on a divided attention test, and it's much more easy to observe this in older individuals than it is in younger. The younger require repeated trials, and they actually start deteriorating in their performance. But if you do it once, you may not see it. The continuous visual memory test, we've replicated some finding of Dr. Fiedler's group as reported, but we've only replicated it in people with lifestyle change. We have not found it in the chemically intolerant without lifestyle change. Those without lifestyle change have more of a problem with the divided attention test. So, people should be aware that there seems to be a significant difference. At the moment, the greater psychological distress ratings have been showing up in the people with lifestyle change, which is really not a surprise.

I'll just fly through this. This is the greater wake after sleep onset in the people with lifestyle change. This is the evidence for increased problems with the divided attention test. This is the evidence of people with lifestyle change do the worst on the continuous visual memory test. Life stress ratings are always higher, particularly in earlier years, in the people who have chemical intolerance. This may be a risk factor. It does not explain anything because there are control groups such as depressed or sexually abused who give similar ratings and do not have the same finding.

Our working hypotheses are that:

- Chemical odor intolerance is a manifestation of neural sensitization;

- Individuals high in this particular marker (chemical odor intolerance) which you can get from self-report, may be especially sensitizable in the laboratory, and we've been able to show that; and

- We can show it if we design the studies properly by using at least 2 sessions. I want to emphasize that for future design discussions over the next few days.

Sensitization, as I indicated earlier, is a process of amplification which does not involve the immune system, and we've seen it. Thank you.

Dr. Claudia Miller, Moderator

Thank you very much. Our next speaker is Dr. James Cone. Jim Cone, currently Chief of the Occupational Health Branch for the California Department of Health Services, and involved in a number of surveillance intervention studies, information dissemination, based in Oakland, California. He has published several articles concerning occupationally acquired multiple chemical

sensitivity, and has interest in a wide range of occupational medicine topics as well. Dr. Cone.

James Cone, MD, MPH
Acting Chief, Occupational Health Branch
California Department of Health Services
Oakland, California

I think the lessons that we've learned from looking at multiple chemical sensitivities in the civilian population, I think, can be applied, and starting with case series. We've looked at cases of individual patients trying to understand their individual history, initiating exposures, and subsequent triggering type of exposures that gives us clues that perhaps pesticides, building materials, perfumes, detergents, and others are high on the list of suspect agents. We then looked at exposure incidence where you have a discrete population exposed to a particular group of chemicals, hopefully a small number. And then look at the outcome in terms of do they produce symptoms of multiple chemical sensitivity, and indeed, there are such episodes particularly in building environmental exposures, particularly to pesticides that I've studied mostly in city and county office buildings, but also in casinos and other settings where there's high incidents of pesticide application while people are actually working in the building.

We've also looked at more cross-sectional populations in particular industries or occupations to see if there are analogous events. And one particular I would draw your attention to is flight attendants. I've been working with flight attendants for 12 to 15 years. And I've looked at different settings where flight attendants were exposed to both pesticides and triorthokerosenephosphate containing oils used in jet engines. And we're seeing a pattern of development of multiple chemical sensitivity like illness in these flight attendants. It's not a specific incident necessarily, but it could be a cumulative, but it may involved in what we call a cabin air quality incident. So, I think there are examples again of, it's not just a single incident, it may be a repeated exposure resulting in the same kind of symptom complex.

And finally, we have population based studies which I think have only recently begun to be done by Iris Bell and others, and Rick Kreutzer and Ray Neutra at the Department of Health Services here in California where we look at not just the people who are ill or the people who come to a clinic, but actually look at the general population to determine is there a prevalence of a spectrum of disease or illness that we could determine. And, indeed, the prevalence that we see in these population based studies is much higher than we would expect, you know, based just on the clinical experience, and how rare this sort of really comes to clinical attention. And I think that's a major lesson, that we may be able to then use some of those same survey type tools in the Gulf War exposed population and begin to look to see if there's something unusual even, or specific going on with Gulf War exposure.

I think in terms of diagnostic approaches, like other diseases where the risk factors are poorly

characterized, and we don't really know what the risk factors currently are, diagnosis is often based on clinical judgement, treatment is empirical. In the setting of the n of 1 trial, as Michael Hodgson has written about on numerous occasions in the setting of building associated illness, is an appropriate diagnostic and treatment tool. It's basically taking the patient's own understanding of their disease, and then combining it with the doctor's understanding, and then developing an individualized approached to try to understand what's going to help this particular patient. I know that's not as sophisticated as a clinical trial that we're all used to, but it actually can help the individual patient.

I find in the multiple chemical sensitivity population that I see in an occupational health clinic, that I have to result to the n of 1 trial. There is no other modality. There is no clinical trial. There are no current treatments that are shown to be efficacious, so as a clinician facing the patient across the table and saying, "I have nothing to offer you," I find that personally unsatisfying and it doesn't really make me feel like I'm contributing at all. So, I think using the n of 1 trial and then accumulating those n of 1 trials is another way of trying to understand is there something we can offer in the meantime until we understand is there a particular etiologic agent resulting in this disease?

The other approach, I think, diagnostically is functional impairment. My patients come and say they have triggers in the environment that they know are predictable. There are things that they know are going to cause a particular symptom, and it's useful in my experience to try to validate that experience. You can validate it in various ways. Some of the ways we've heard here are using fairly sophisticated sociological and neuropsychological techniques. One that I've used is simply a neuropsychological test battery administered before a simple challenge with one of the agents that somebody knows triggers their symptoms, and then repeating those neuropsychological batteries in a maybe different form so you don't have a learning effect. But, it's a way of validating that something indeed is different pre- and post-trigger that's useful, as well as other pre- and post-challenge testing. I think this is well developed in the pulmonary field, but we haven't really necessarily used this, because I think it's difficult. Sometimes I've had to hospitalize my patients to be able to undertake these in the face of some of the severe reactions that some patients do have. So, it's not an easy task, but it can be done.

I think as Ray Neutra in his study using the California general population Behavioral Risk Factor Study proposed we look at the multidimensionality of these diseases, not just the all or nothing approach we've traditionally used for disease. And measuring multiple dimensions using tools like Claudia Miller's brief questionnaire looking at chemical intolerance, alcohol and food intolerances, degrees of masking by cigarette smoke and caffeine and other agents, and then try to understand that many of our patients are on a continuum. And I think that's already been discussed today, that really we can see MCS as a continuum, that many of us have some aspects of MCS that really don't reach the clinical threshold, but under certain circumstances like being sent to a foreign country and being exposed to a multiplicity of agents we've heard about today,

may bring out this particular disorder or a similar disorder that as of this moment we cannot clearly define.

So, my time is up. I think Gulf War syndrome like any other disease cannot be diagnosed or treated effectively by a clinician who doesn't believe that there is such a disease, refuses to take an appropriate history, and labels the patient psychotic without any kind of psychiatric work-up or further investigation. So, I think we have a challenge as clinicians. We need to educate clinicians to not go down this path. We really have to have some open minded clinicians out there willing to at least ask the questions, and listen to their patients. Thanks.

Dr. Claudia Miller, Moderator

Thank you, Jim. Next is Dr. Richard Graveling who is head of human sciences at the Institute of Occupational Medicine in Edinburgh. He visited us from a long distance a way. His interest in chemical sensitivity really stems from the Institute of Occupational Medicine, being commissioned by the British government to produce a scientific review of the published literature on this topic which has just come out in *Occupational and Environmental Medicine*. He is the first author on the subsequent review of this review, and is here to, I guess, learn from what we're doing here in this country. Maybe he can shed some light on what we need to be doing. Dr. Graveling.

Richard Graveling, PhD
Head, Department of Ergonomics
Institute of Occupational Medicine
Edinburgh, Scotland

Thank you. Good afternoon everybody. As you've just been told, I'm here from the Institute of Occupational Medicine Edinburgh, Scotland. Probably most of you haven't heard of us. We're an independent research center. We're a World Health Organization collaborating center for occupational health, and we are interested in, particularly in research and consultancy, in a wide range of occupational and environmental health problems.

We were commissioned to carry out a scientific review of the literature on MCS on behalf of the U.K. Health and Safety Executive. That was as a result of a limited tendering exercise. You'd have to ask them why they asked us to do it. I'd like to think it's because we're renowned for our independence. We had no prior particular position on this. There were a number of people in the U.K., for example, who are involved in this field, but inevitably whatever they came up with, whatever their response, then there would have been some people who would have felt, "Well, they'd have to say that wouldn't they?" Having said that, we're not completely unaware of activities in this area, and we are currently involved in research into organophosphate exposure in sheep dippers.

We were asked two specific questions. First of all, is there convincing evidence that exposure to chemicals, including pesticides, can result in some people in a clinical response to very low doses of that chemical or structurally unrelated chemicals, and what is the evidence that any such reactions are a consequence of physiological processes or psychological factors? That is, explanatory mechanisms. Very briefly, I suppose the first thing can be summarized as does MCS exist, and not merely a manifestation of psychological psychotic disorder? Our conclusion, having looked at the literature was, "yes, but . . ." which I suppose is understandable.

The definition and diagnoses used in a lot of the literature is very varied in quality, and sometimes objectivity. Coming at it from an independent scientific point of view, obviously a lot of the qualitative exposure data was very patchy and the quantitative exposure data was almost non-existent. In the U.K., there is no prevalence data at all as to how big a problem this is. Many of the people that I am aware of . . . I think it's included as . . . they see themselves almost as having multiple allergies rather than necessarily having this label of multiple chemical sensitivity. And there's an impression that that's somehow become a rag-bag of a convenient label for problem patients by some physicians. That doesn't help because, of course, in amongst those "problem" patients there will be people who do have genuine psychiatric problems. They may have other sensitivities as well, but they do have these problems. Nevertheless, our feeling from the literature was that, yes, this problem is a real problem, which I think was an important thing. It wasn't necessarily what the Health and Safety Executive wanted to hear, but nevertheless that was our conclusion.

As far as mechanisms for causing MCS were concerned, we reviewed, I have to point out if I've offended anybody in the audience in terms of not mentioning their work in our review, we actually looked at a lot more papers than were actually cited in the journal paper. Clearly, there are a lot of different mechanisms invoking different aspects both of psychology and physiology, or neurotoxicology, whatever. The psychology ones are very interesting in terms of the approach that people seem to adopt. Quotes like, " After exclusion of toxic and primary immunological and psychiatric causes, it should always be assumed that MCS has a psychological etiology." And another suggestion that struck me as rather illogical was, "It must be psychological because subjects only attribute symptoms to chemicals that they are aware of." Well, how they're expected to attribute symptoms to chemicals they're not aware of I don't quite know.

The outcome of all of this was that we didn't feel that the evidence, that there was any unequivocal evidence for the various immunological or respiratory or mechanisms that had been presented. Interesting enough, and I have to say this even though I am sitting a short distance away from her, that the one mechanism that we came out as offering the most promise was that of the limbic system, limbic sensitization. It was interesting, maybe because it's a relatively new theory in comparison to some of the others, but it was the one theory which hadn't got negative papers. ***Yet***, perhaps yes. So that, yes there were the proponents of the immunological theories and then there were also the detractors from such theories, and likewise for various psychological

theories.

I think we have a big problem in the U.K., and I think the Health and Safety Executive have a problem in that, and I'm not speaking on their behalf here when I say they don't really know how to take things forward. One of the things they don't know is how big a problem they have. From the literature we identified estimates of prevalence suggesting that estimates of 1 percent were gross overestimates up to 20 or 30 percent of the population are interested to hear the figure put forward earlier of about 3 to 5 percent because that seemed, obviously, somewhere in between.

So, we're still learning. I think we're certainly some way behind you. But, hopefully, we will learn from your mistakes and misdirections in the past, and together we can take this forward. Thank you very much.

Dr. Claudia Miller, Moderator

It reminds me of what Winston Churchill used to say, "Americans can be counted on to do the right thing, but only after they've exhausted all the other possibilities." The next speaker is Dr. Meggs. Bill Meggs is Chief of Medical Toxicology and Vice- Chairman of the Emergency Department at East Carolina University, and he's had a long standing interest in chemical sensitivities. His areas of research include chemical induction of asthma and rhinitis, airway problems associated with MCS and sick building syndrome, and organophosphate poisoning. Dr. Meggs.

Richard Meggs, MD, PhD
Associate Professor of Emergency Medicine
Vice-Chair for Clinical Affairs
Chief, Division of Toxicology
Department of Emergency Medicine
East Carolina University School of Medicine
Greenville, North Carolina

Thank you Claudia. Rather than show you my latest greatest data, I thought I would use my 7 minutes to editorialize and make 7 quick points.

First, some people want chemical sensitive patients, to have chemical sensitivity you have to have some documented acute exposure. And I think you can forget that because there are plenty of people out there who clinically look the same to me and they have no documented exposure.

Second, patients with chemical sensitivity have documentable medical diagnoses. There's a very high prevalence of rhinitis in this group. They have asthma, irritable bowl syndrome,

musculoskeletal and collagen vascular diseases, neurological and psychiatric disorders. So, if you want to say, "Well, we're going to exclude anybody with a diagnosable medical illness from having chemical sensitivity," you're really throwing out the baby with the bath water.

Avoidance is very important in this group because they have ongoing inflammatory processes often, and you have to get them out of the chemicals, or else they're going to progress from inflammation to fibrosis. This is best documented, for example, in patients with asthma who can progress to COPD if they continue to be in a workplace where they have chemicals that are causing airway inflammation.

A lot of people looking at chemical sensitivity now are really hung up with the back end of the illness, and they've totally forgotten about the front end. And the front end of chemical sensitivity is patients with chronic, diagnosable conditions, often with an inflammatory component, and no acute reactivity to chemicals. And through a process of de-adaptation, the inflammation decreases and they develop this reactivity. And this has been demonstrated over and over again in the clinical setting. We really need to study that process in a more formal way. But it's very important to appreciate that, and the importance of adaptation in chemical sensitivity.

I would comment that people who are studying psychiatric problems, in particular depression, in association with chemical sensitivity must control for allergy. It's very well known, there's a very strong literature looking at both ends of the association between atopy and depression. If you look at psychiatric admissions for depression and skin test them, as many as 90 percent in some studies, but greater than 50 percent, and many times higher than people admitted for schizophrenia, have allergy. And also there's a strong association between chemical sensitivity and atopy. In my clinic, when we skin test people who come in with chemical sensitivity, there's a very strong association, and that data we'll becoming out with. So, if you're studying depression and chemical sensitivity and don't control for allergy, you have a very strong chance of doing a totally invalid study.

Just another couple of more political comments. I've been coming to, Claudia said I have a long interest in chemical sensitivity, I think it's 10 years now that we've been coming to these meetings. And over and over again, we've made a strong recommendation, or the participants at the meetings, and I sat at one of these meetings and saw Dr. Albert Taylor and Dr. Bill Rea agree, I never thought the two of them would ever agree on anything, but they agreed, and we made a strong recommendation that we need a national laboratory where we can do controlled studies in a residential setting where people are removed from the chemical environment for 24 hours a day, and look at people with disorders such as rheumatoid arthritis, and asthma, and lupus, and all sorts of inflammatory conditions to see what role this low level of chemicals play. This recommendation keeps being made, and I hope that at some point it will be acted on. Because we really need this. If this hypothesis is true, it has profound implications across all fields of medicine in terms of treatment of diseases that we really don't have as good of treatments as we would like.

And one last comment. There's a book that everybody will probably enjoy. It's called *The Heat is On*. It's by a German journalist. He takes on the issue of global warming, which is highly controversial. And he says, "Well, why is this controversial? 1998 was the warmest year in history, and '97 was the second, and 1998 had more carbon dioxide in the air from fossil fuel burning." And he says the reason it's controversial is there's a cadre of 10 or 12 people out there, and he names their names, and their associations, and their funding, who are funded by commercial interests who have an interest in continuing to burn fossil fuels. I would suggest that if there is a journalist out there who wants to look into the possibility of having a book, that he could look at the possibility of maybe there's not a cadre of people out there who are representative of some commercial interest who do not want this chemical sensitivity thing to become as big as it potentially could be, and see if there's, you know, you could find some people like that. Maybe you can, maybe you can't. I don't know. And I'll stop with that.

Dr. Claudia Miller, Moderator

So, Bill, are you saying when you hear it's not about money, it's about money? Anyway, that's actually a line from the impeachment hearings. The next speaker is Dr. Anne Solomon. She received her doctorate actually in religious studies, and she's now a doctoral candidate in behavioral medicine in clinical psychology at the University of Maryland, Baltimore County. Her dissertation title it *Neurocognitive Performance in the Multiple Chemical Sensitivity Syndrome*, and I believe she is working with Dr. Bascom. Dr. Solomon.

Anne Solomon, PhD, MA
Research Fellow, Department of Medicine
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Thank you very much. I want to be certain that the neurocognitive data is not overlooked, reduced, dismissed, whatever. I consider it to be extremely important because, in fact, according to Miller and Mitzel's survey, it is the most prevalent symptom. In my own review for my dissertation, of approximately 50 unique patient samples, it was ***the*** most prevalent symptom. What does this mean? It means, of course, that many things can contribute to it. But it also means, as we heard this morning from one of our Persian Gulf War vets, as her mental sketch pad began to disappear from her life, her daily life was heavily impacted. And any therapy, any treatment, is highly dependent upon the person's ability to follow through on it. So that their cognitive state is extremely important.

I would also like to acknowledge, given my own background in the Baltimore VA which I had the opportunity as an intern to evaluate Persian Gulf War vets, and at Johns Hopkins as a pre-doc intern in medical psychology, where we worked with, we hoped, reversible dementia kinds of assessments, that there are not very many good neuropsych instruments at the moment for

evaluating right frontal function.

And so, following up on Dr. Bell's suggestions that the EEG data suggest that there is a problem with sustained visual attention and executive function, we can now be more specific in our evaluations. So, what I would like to describe for you is my dissertation research study which is still going on, which perhaps can offer a kind of paradigm for doing neuropsych research in which elements such as depressive symptoms taken on the day of testing can be co-varied out. The level of fatigue, which we know correlates with a routine type of concentration test, can be factored out. The Chemical Intolerance Index, which Dr. Bell has developed, which we have administered also to a control group of asthma patients, which for them is very high, but on this sustained attention task, their performance is normal. So, we have also perhaps removed some of that irritative inflammatory side and the lesion stems. So, this is the kind of research that I would suggest needs to be done next, something along these lines, more specifically then.

Our study involves a civilian population who are not highly stressed, they are not terribly high on depressive measures, but they have some. And I think it's crucial to include civilian groups within all of our future Gulf War research. Why? Well, if people are tremendously stressed, and we're having to work in new areas where we're working with exclusionary diagnoses, it is just still, as we all know, too easy to blame the stress. If we have civilian populations, like in our study, who are not terribly highly stressed and yet have these cognitive problems, then I think we are on the right track in really figuring out what's going on.

We have also a comparison group of PTSD patients who are veterans. Their situations are much more complex. But, their characterization is important, just to compare them with the other groups even if for various reasons, because some of them have asthma in addition to other problems, they cannot enter into the final diagnoses, at the final statistical analyses their characterization in comparison is nonetheless extremely important.

Next, appropriate medical control groups. I would suggest that there are several subtypes within these neuropsychological problems. One subtype that we're concentrating on are the pulmonary people. But, we have within them some people who have both nasal symptoms and the dermatitis/cardiovascular, for example, subgroup. Their neuropsych profile is not exactly the same. All right? It's not exactly the same. We have to be very careful now. We can now begin because we have specific tests, specific areas to test. We have to be able to differentiate them.

Now, in terms of the actual type of test, it is a sustained non-verbal learning and memory test that we are using in which the average means for both the MCS civilian population and the Gulf War group is about 20. Whereas, for the asthma and for the normal groups the mean is about 40. That is an enormous difference. It cannot be explained by the depression, or the stress, or the Co-Cause Mean Index either. It stands alone.

This is a preliminary result because we haven't finished with all of the data collection yet, but we are a good way through towards the end. We have about another month yet to accept people. It is a computerized test. It is a test which is capable of having multiple forms developed, and that is another extremely important element of all future neuropsychological testing as some have suggested, and as I would certainly recommend. Thank you for your attention.

Claudia Miller, Moderator

Thank you. Our next speaker is Dr. Roberta White. She is a clinical psychologist with specialty training in clinical neuropsychology. She directs the Clinical Neuropsychology Department at Boston VA Medical Center where she heads up the training program in neuropsychology. Most recently her research has focused on intellectual and mood effects of exposure to industrial toxicants, but even more specifically as research director for the Boston Environmental Hazard Center looking at the neuroimaging genetic correlates of Gulf War related health symptoms in multiple chemical sensitivity.

Roberta White, PhD
Director, Boston Environmental Hazards Center
Director, Boston VA Medical Center
Boston, Massachusetts

Thank you, Claudia. I'm also going to talk about neuropsychological testing. For the purposes of this talk, I'm wearing my clinical hat. I'm going to be talking about some of my experience with neuropsychological assessment in civilian populations with MCS. I'm going to present some clinical data this afternoon. These data were collected on patients who were referred to an occupational and environmental neurology clinic for assessment of cognitive deficit secondary to exposure to neurotoxicants. The subjects whose data I'm going to show you were chosen to be a subgroup who had no medical conditions or developmental disorders that would affect cognitive functioning, and they're simply here to provide an example of what I think the problems are with using, and the advantages are, with using neuropsychological assessment in the MCS population.

So, the first overhead shows you the demographic composition of my sample. There was no difference between the MCS patients and the controls in terms of their performance, basically on tests of estimating premorbid function, vocabulary and information. On the next overhead we have a summary of comparisons on some tests that assess attention. You can see that for digit spans, reciting digits backward and forward, the MCS patients had more difficulty. They performed lower on an omnibus attention measure from the Wechsler Memory Scale-Revised than the controls. But they performed about the same on the trail making test and their ability to do oral arithmetic items on the Wechsler arithmetic test was about the same as controls.

In terms of executive function, their ability to arrange pictures to tell meaningful stories and to

complete block designs was worse than the controls. Please note on this overhead the difference when you look at raw scores versus the scaled scores. I think you get too much restriction of range when you use scaled scores in this kind of data. Very interestingly on controlled word association tests, the MCS patients did better. This is a test in which you have to produce words under structured conditions and they did better than controls. They were worse in an inferential reasoning test called the Wisconsin Card Sort, and performed about the same on some reasoning tests from the Wechsler Adult Intelligent Scale.

In terms of memory function, the MCS patients scored lower on all the omnibus memory tests from the Wechsler Memory Scale-Revised including general immediate recall index, verbal index, visual index, and delayed index. The difference, interestingly, on the delayed index was not significant between the MCS patients and the controls, and moreover, what MCS patients are showing on this and other tests that I'm going to present in terms of the memory domain, is that MCS patients, once they learn information, are able to retain it. It's sometimes difficult for them to get at it as readily as they would like, but it doesn't disintegrate, it doesn't disappear. It remains in memory store.

Difficult paired associates, 10 paired associates low in associative value, were also performed better by the MCS patients from the controls. And, interestingly, on word triads, a test in which the patient is given a series of words, then they have a distraction task in which they have to count backwards, then they have to repeat the words, the MCS patients performed nearly as well as the controls. So, on some of these challenging memory tests, they did pretty well.

The next overhead shows a delayed non-matching to sample. This is an animal model test, often we hear calls to use animal models in our studies. The MCS patients and the normals performed about the same.

In terms of motor function, the MCS patients were slower on digit spans, I'm sorry, on digit symbol, a coding test, but not to a significant degree. But their finger tapping and their ability to use a pegboard called the Santa Ana Pegboard was slower.

In terms of spacial functioning, the MCS patients were identical to the controls in identifying missing parts of pictures on a task from the Wechsler Adult Intelligent Scale. And they were slight slower in putting puzzles together, but just as accurate.

In terms of language functioning, there were no differences on the neuropsychological language tests between the MCS patients and the controls.

In terms of mood and personality testing, on the Profile of Mood States, not surprisingly, MCS patients expressed significantly more dysphoria than controls. On the MMPI, the MCS patients showed more of a tendency to expect a lot of themselves, that's how I interpret their higher score

on the L-scale, more psychiatric symptomatology, more physical symptoms, and more depression and anxiety. And those findings just simply repeat something that Nancy Fiedler, she's already done this twice before, and better than I'm doing it today I have to comment.

Okay. What do these results mean? Now, what I want to show you now very briefly is some data from an individual patient. And, I'll probably just show you a couple of sets of her scores. But I think they will tell you something about why we see, some of the reasons we see the differences and some of the need for caution in using neuropsych methodology in MCS studies.

In terms of general intelligence, this patient had above average intelligence. Let's focus on the attention overhead which is next. You will see that we gave her digit spans twice. I always give my patients digit spans twice to see how consistent they are. The first time we tested, she did the digit spans, her digits backwards were better than her digits forward, which was unusual. The second time she was given it, she performed better on digits forward, but worse on digits backward.

Her visual spans forward pointing to a spacial array were equal forward and backward. She performed very, very well on trails which is a challenging attentional test, but she had a great deal of difficulty with the continuous performance test. I'm going to skip the rest of her overheads. What we basically see in her data is a lot of variability in her capacity to do tasks between and within tasks.

And, I think in summary I should just say that, on neuropsychological testing, MCS patients do perform more poorly than you would expect. It's very difficult to make domain-specific predictions about that. There is no signature pattern of poor performance on neuropsychological tests that would allow us to diagnose MCS the way we can for some toxicants. And, I'm very interested in looking at this variability in performance in terms of what happens on functional imaging as the brain is working on these tasks.

Dr. Claudia Miller, Moderator

All right. We're running just a few minutes late, but I want to take about 5 minutes worth of questions. The next panel is a little bit smaller. So, we'll take a few questions. Please try to keep them to one sentence if you can.

Discussion

Robert Feldman, MD
Boston University School of Medicine
Boston, Massachusetts

I have very brief questions. Number one, with regard to Dr. Bell's description of the electroencephalographic studies, I'd like to know how she can explain the relationship between a resting alpha increase in height in a situation where there's a hyperalert state and increased attention or difficulties with the sleep disorder with regard to how those are controlled for. As a neurologist, I would expect the alpha to be suppressed in those individuals. The next question with regard to the panel quickly, Dr. Graveling, is MCS common? I think you mentioned this in the sheep handlers, and what do you think of Peter Behand's study of chronic fatigue syndrome in the sheep handlers? And Dr. Cone, any of your patients get better? And Dr. White, how would you explain, which test would you use to elaborate upon Dr. Bell's concept of mesolimbic? In fact, is MCS common in simple partial epilepsy?

Dr. Claudia Miller, Moderator

That was the longest sentence I think I've ever heard. All right. We've got multiple questions here. They're all very interesting questions. I'll ask the people to respond starting with Dr. Bell and going on down. But, please, in the future everyone else stick to one question and then consult the others on the panel.

Dr. Iris Bell

I agree that the issue of the paradoxical increase in alpha is extremely interesting and confusing. However, we have found in the literature that sensitization of animals to cocaine, I believe it is, produces an inversion of specifically alpha I and alpha II activity on spectral analysis in the animals once they've been sensitized – not before they've been sensitized and not during the process. And so we believe that what we're looking at are people with established sensitization. That's our best explanation, but what that really means, because it does not fit with the behavioral picture, I don't know right now.

Dr. Richard Graveling

We are studying specific neuropsychological disorders in people who have been handling sheep. We have not actually looked at MCS specifically in this group. And, it's my colleagues at the Institute who are primarily involved in this work, and I'm not personally involved in that, and I wouldn't like to comment therefore on the work on CFS.

Dr. James Cone

I think the question of improvement does pose a problem. Number one, there aren't longitudinal cohorts that I'm aware of that are being followed other than kind of clinical case series as I mentioned. Those anecdotally patients I followed, of course, patients come back, and there are ones who are getting better, there are ones who tell me they are getting better. But the ones that

don't get better, they go see somebody else I'm sure. So, it's a little hard to answer that question. I think we need to have a longitudinal cohort or surveillance for answering that kind of question. I don't think I can answer it just based on limited anecdotal clinical data.

Dr. Beatrice Golomb

My question pertains to regional cerebral blood flow with and without challenge. There was one small unblinded study in Gulf War veterans without predefined criteria that claimed that 6 of 6 Gulf War veterans with chemical sensitivities had abnormalities on SPECT, while none of the control, and also there's some anecdotal data reports that SPECT abnormalities increase in subjects with exposure to their sensitizing chemicals. I was wondering if there was any ongoing work in that or if any replicating data is available? Who is involved in the neuropsychological aspects?

Dr. Roberta White

Howard Hu is doing work on that right now. The problem with the SPECT is that it's very difficult to localize the SPECT abnormalities. The SPECTs are read as abnormal, but they're not all abnormal in the same place. And we're doing functional imaging. It's not quite SPECT, but it's similar. We can't do challenge yet, but we plan to in the future.

Leslie O. Simpson, PhD
Red Blood Cell Research Trust
Dunedin, New Zealand

Madame, I'm disappointed that a discussion is a 2-way thing. Your time constraints mean that the feedback, which Congressman Sanders suggested we needed, isn't taking place.

Dr. Claudia Miller, Moderator

I apologize for the way it's structured, but I didn't do it.

Dr. Leslie Simpson

The point I want to make is that the conditions that we've been discussing and heard discussing, are what I call the dysfunctional disorders, because we have not addressed why MCS resembles what you people call chronic fatigue syndrome, which I don't accept. I talk about myalgia cephalmyalitis. How does this relate to fibromyalgia? The common factor lies in the field of blood rheology. And there are changes in the blood cells of all these groups in 6 different countries, in 4 different countries relating to Gulf War syndrome. They have a blood flow problem. Why should one expect that they have normal psychological function? Why should

muscle function be expected to be normal? I think we're looking in the wrong direction. Thank you.

Dr. Claudia Miller, Moderator

Thank you for your comments. I want to point out that we'll have lots of time in the group sessions, and I hope you'll raise that in whatever session, if you're in the treatment or diagnostic group. If you're in the sessions where there is discussion, the purpose of breaking up into smaller groups was just so that your ideas could be included in that discussion. Next.

William Baumzweiger, MD
Los Angeles, California

I wanted to ask why, if anyone has any idea, is the limbic system involved? What is the mechanism of that involvement? I mean, I have my own ideas, but I'm wondering what your idea is why the limbic system and brain stem are involved in all of these conditions? What is the causal relationship between whatever preexisting or precipitating factors causes the limbic system to always be involved?

Dr. Iris Bell

That's a very good question, and again, we don't have any full answers. Within the sensitization model, the very simple answer is that the nose is connected to the brain, there is no blood brain barrier, the amygdala which is a key way station within the limbic system is one of the first locations to receive information from the nose, from the olfactory bulbs. It and the olfactory bulbs are highly sensitizable to the point of kindling, to the point of temporal, presumably to the point of temporal lobe seizures. And so, if an odor of some sort were capable of doing a 1-shot hit on the limbic system and inducing that process, which has been shown I believe with corticotropin-releasing hormone, I don't whether it's been done completely with chemicals, or by intermittent repeated exposures. You end up with an altered state which in animal models has been shown to be permanent. Once that's dysfunctional, you have regulation of the rest of the body dysfunctional, because it regulates immune function, endocrine function, autonomic function, and psychological function. That's the simple answer.

Dr. Claudia Miller, Moderator

I'll take one more questioner. Will you tell me to whom that's directed? Could we get the next panel to come up here, and I'd appreciate everyone's help.

Audience Member

Well, I think to Dr. Bell. I appreciate Dr. Meggs comment also on etiology because I think, Dr. Bell, you start trying to talk about etiology and I think that's important if we're going to get back to Gulf War syndrome in terms of what are the mechanisms? Because we don't understand the mechanisms. I don't think we have the basis for relating it. But, one thing that it seems to me is we didn't talk about the cholinergic stress response. This, you know, if a non-smoker bites down on a piece of nicotine chewing gum, or an injection of physostigmine will give you this feeling of being terribly sea sick, and which of course all your sensitivities, all sorts of smells go up tremendously. That could be related to some sort of sensitization mechanism. But, I think it's important to get to some sort of actual mechanisms. And of course if you got to the cholinergic stress responses, then you could get back to the specific mechanisms related to the organophosphates, sarin, nerve gases, or other factors. Then you could start seeing what is the actual underlying relationship between this chemical sensitivity and the syndrome that we're looking at in the veterans.

Dr. Iris Bell

One very important point about that is I agree there may be some specific associations, but if you look carefully at the symptoms that the veterans are reporting, as are the civilians with MCS, there is less specificity to them. They are a pattern of symptoms, but people with similar chemical problems may have different manifestations, and people getting the same manifestations may have different chemicals as strong triggers. It could be an individualized registration within the brain and the rest of the body. So, you're not going to find a one to one correspondence to a toxicant. I think a very important point people have made is you have a multi-factorial problem and you must do your design, your methodologies, appropriately to accommodate multiple etiologies simultaneously. Cholinergic stimuli of the type you talked about have been shown to lower the threshold for kindling, so if I can keep bringing it back to sensitization, it certainly could be a factor, it could be an initiating factor as could many of the factors that the veterans were exposed to in the Gulf. Once you're initiated, then you get elicited at low doses.

Dr. Claudia Miller, Moderator

Thank you, and I think our next panel is assembled. We appreciate the questions. The first speaker, this is on the experience of patients and physicians with MCS, is Dr. Rebecca Bascom. Dr. Bascom is a Professor of Medicine at Penn State University College of Medicine, and Chief of the section of Pulmonary, Allergy, and Critical Care Medicine in Hershey, Pennsylvania, having recently left Hopkins. Dr. Bascom.

MCS: The Experience of Patients and Physicians

Rebecca Bascom, MD, MPH

Chief, Pulmonary, Allergy, and Critical Care Medicine
Professor of Medicine, Pennsylvania State College of Medicine
Hershey, Pennsylvania

Actually, I recently primarily left the University of Maryland, although I also had a joint appointment at Hopkins. That was the first decade in Baltimore was at Hopkins. Second at Maryland. Now I'm in the chocolate capitol of the world, and I think if anyone who has a kid under 10 wants to come visit and take their kids on the roller coaster, just let me know, we'd be glad to give you an excuse to write off the trip.

When I was a fellow, I got sent to see my first patient who had multi-system complaints triggered by low level exposures. And I remember talking to someone later about how inadequate I felt as a clinician and they said, "Well, would you like to be the expert?" And I remember I almost burst into tears at that point because I felt that was so impossible. It just shows how little we know that now I'm sitting up here as someone who supposedly has experience in this area. I don't think I'm really a whole lot better at taking care of this conditions. So, I echo Congressman Sander's frustration in this regard.

I have 3 points. One, what makes a problem patient? I think very clearly patients that meet the definition of MCS elicit nods of the head, and they're categorized as a problem patient. A problem patient basically is one who hopes for a better result or expects a better result than you as a clinician think you're going to be able to deliver. Therefore, the essence of the problem is that we don't have a good dose of penicillin for this particular form of strep throat or whatever it is.

Number two, I for one was very impressed with the Department of Defense funded and the Veterans Administration funded research that was presented in the previous two panels ago. Because I think what that said to me is that we actually are beginning to have some sense of the magnitude of this symptom, and also of its dimensionality, and that we know that it is, that reporting be especially sensitive to chemicals. Something that the EPA study first looked at in the context of the Waterside Mall. And that showed up about 25 percent I think then. Now this number of 25 or 30 percent of people saying, "Yeah, they think they're especially sensitive." That number seems to be popping up. So, we have that number, and that suggests that this is not an uncommon problem. And then unusually sensitive, I think by now we have 3 or so sets of evidence that if you ask somebody, "Do you consider yourself unusually sensitive," I think I'd be interested in the people that did the study making a table for us and see if we can get a number of 8 percent, maybe, 10 percent. And also the, people then who are avoiding or changing their lives because of it, that's maybe 2 to 3 percent. And at least, my look at the data that were presented, suggested that the Gulf War experience increased the odds that a person would be changing their life because of these kinds of symptoms.

Now, I know that the pharmaceutical company that worked on Viagra thought that they had a

good product on their hands, and they estimated how many people were going to use it, and they did the estimate based on how many people came to their doctor complaining of erectile dysfunction. But I also know that when the drug hit the street and people had the chance to try this to improve their functioning, that it was a much greater seller, it was much more popular than people had predicted. So, I think when you have a complex symptom that gets at what's important to people in their lives, and they don't really want to talk to a doctor about, especially if they don't think there's anything to be done, I think that of course we don't see it, of course we see only a tip of it, a small proportion. But I also think that the pharmaceutical industry has a huge opportunity here, because I suspect that there are ways to treat this fairly rapidly.

How should we should we find those? And this is my last point, which is this n of 1. You know the drug, there's a medicine called Zyban right now, buproprion, Mel Gibson told David Letterman that it's what got him off his 3-pack a day habit. Okay? Great drug. And a lot of people have quit smoking with the assistance of buproprion. Well how did they find out about that? It's because a psychiatrist was treating patients for depression and noticed that these patients, all of whom were heavy smokers, were quitting smoking. She couldn't believe it, so she called up the pharmaceutical company and they said, "Oh, yeah, right." So she said, "Okay. Well, I tell you what, give me a placebo, you know 20 cases of placebo and 20 of the drug." And she tried it and got these good quit rates. So then they tried another small pilot study and they got similar improved results. And so as a result they did the huge studies that now show that buproprion, Zyban, is very effective in getting people to quit smoking. Now, there are zillions of drugs out there that lots of people are taking for lots of different reasons. And if the people who gave us studies where they used some kind of definition of chemical sensitivity could give us some kind of a simple scale that could be applied in all sorts of pharmaceutical studies, then I think we would see if there are any that cause a shift in people's sensitivity, and that would begin to give us our clues for this condition. Thank you very much.

Dr. Claudia Miller, Moderator

Our next speaker is Dr. Leslie Israel. Dr. Israel is actually Assistant Professor of Medicine and Director of Employee Health Services at UCSF. She's been involved in the clinical assessment and management of patients with multiple chemical sensitivity there.

Leslie Israel, DO, MPH
Medical Director, UCSF-Stanford Employee and Occupational Health Services
Assistant Clinical Professor, Department of Medicine
University of California, San Francisco
San Francisco, California

Good afternoon. I would like to thank Dr. Drue Barrett for extending an invitation to me to participate in this conference on behalf of my colleague Dr. Robert Harrison from the University

of California, San Francisco who was unable to attend.

I intend to address the experience of patients and physicians in the clinical management of multiple chemical sensitivity. The clinical management begins with a history and physical, and the physician needs to do various things in that history and physical. That is, rule out an occupational or non-occupational cause, obtain detailed occupational and environmental history of exposures, and determine if short-term removal from the workplace, exposure, or exposures is indicated. Again, you want to do a history and physical, and I mentioned these things here.

So, what I'd like to do briefly is review two cases. These cases, I expect, will generate further discussion at a later time. A 48 year old disabled nurse calls to request a prescription for Medicare paid home oxygen treatment for multiple chemical sensitivity. After her previous physician has retired from practice, what does the doctor tell her?

- "MCS is not a recognized disorder and oxygen treatment is not appropriate." I think we'd all agree that this is an inappropriate statement to make.

- You would send a prescription in the mail for home oxygen. This physician apparently has not seen this patient and, therefore of course, you want to meet face to face with your patient and find out the history of oxygen use.

- You refer her to another physician who treats MCS. Of course if you don't treat MCS that's appropriate.

- You will make an appointment to see her (which was done).

She presents wearing a cartridge respirator, speech is slurred, and affect is dull. History is sketchy but she has been severely limited for years by reactions to a wide variety of environmental irritants. Physical exam is normal. She requests prescriptions for vitamin and mineral supplements. What does the physician do?

- You refer her to a neuropsychologist for evaluation and treatment. This has been discussed, and yes, this may be an appropriate step given that she has slurred speech and we have not gotten a history, which is something you will do.

- You give her a prescription for home oxygen and vitamin supplements. I won't go into the criteria for home O_2 but this may be indicated in this case.

- You advise her that you have nothing to offer and decline further treatment. Of course this is inappropriate.

- You begin antidepressant medication. If, in fact, she appears clinically depressed and the neuropsych evaluation supports that or doesn't support it, you may decide to do this giving symptomatic relief for her depression, we hope.

This is the next case. I'm going through these quickly. A 37 year old man presents with a 12 month history of progressive myalgias, fatigue, headache, and memory loss. He works as a civilian machinist at a federal shipyard and has been exposed to organic solvents for 9 years. Over the past 4 months, he has noted increased fatigue, forgetfulness, and myalgias when in clothing stores or when exposed to perfumes or gasoline fumes. Physical examination is normal. A previous physician advised him of immune dysfunction with low levels of chemicals in his blood. What does the good doctor do? You decide to request a neuropsychological evaluation which shows depression with moderate cognitive deficits consistent with organic brain dysfunction. He has been transferred to an outside maintenance job without solvent exposure. He feels relatively well when he avoids low level exposures, but even in his modified duty position cannot avoid automotive exhaust fumes. He decides to move to the beach near the Oregon border and request disability. What does the good doctor do?

- You refuse to put him on disability and recommend a primary care physician close to his new residence. Well, in fact, he is not able to perform his job as a machinist. Disability needs to be addressed in this person. Recommending a primary care physician close to his new residence may not address his MCS or his work-related needs.

- You place him on disability and refer him for cognitive retraining. That might be an option.

- You place him on disability and begin antidepressants. In fact, if he is depressed, this again might be an option.

- You contact his employer and discuss another modified duty position. This gentleman has told you he has plans to move to Oregon. It's very important to have the patient have a sense of being able to feel in control over their environment and over their decisions. He has made a decision and you want to be supportive of it. This may be a cleaner environment, and healthier for him.

So, in summary, these are some of the things that are important in dealing with a patient:

- Non-judgmental supportive therapy;

- Avoidance or reduction of odors or irritants;

- Enhancing the patient's sense of control, and this may done through exercise, physical

therapy, meditation, and other modalities; and

‘ Biosensitive feedback and so forth or other options.

Therefore, in conclusion, I want to say that these clinical management options are key to successful treatment of MCS patients. Thank you.

Dr. Claudia Miller, Moderator

Thank you. Our next speaker is Ms. Mary Lamielle who is Executive Director of the National Center for Environmental Health Strategies. And she edits *The Delicate Balance*, a patient newsletter. She has done a great deal to advance accommodations for both housing and for employment under Americans With Disability Act to help patients with MCS. She is also a member of the President's Committee on Employment of People with Disabilities. Ms. Lamielle.

Mary Lamielle
Executive Director
National Center for Environmental Health Strategies
Voorhees, New Jersey

I'm going to talk briefly both with regard to patient and advocate frameworks. Twenty years ago now, in 1979, I became hypersensitive to chemicals. I didn't know this at the time. I didn't understand what was happening. I didn't know why I was so sick and getting sicker by the day. I didn't know how to improve my situation until 6 years later when I finally saw an occupational health doctor who was familiar with the phenomenon. He had been seeing numbers of patients who worked in the pharmaceutical industry and who had gotten sick from dusts from the various pills that were being manufactured. He recognized what was going on with me, and that was my first connection with how to deal with this.

In 1979, I had multiple community and indoor exposures. We lived in sort of a fog of diesel fumes and a malfunctioning sewage treatment plant, had begun a major household remodeling project, had the pesticide Dursban sprayed into our bedroom walls several times for an insect problem, and actually had problems with our heater backing up to the house. Subsequent to that, for nearly 14 years now I have been an advocate for those sick, injured or disabled by chemical and environmental exposures.

As Director for the National Center for Environmental Health Strategies, I pretty much work to keep healthy people healthy, and to help those sick or disabled achieve a reasonable quality of life. At the center, we receive anywhere from 500 to as many as 2000 requests for information a month from phone calls, correspondence, and e-mails. The majority of the patient requests are in one area – medical – the search for health care, diagnosis, treatment, and a cure, and

compensation is relevant. I'm sure that search is the same whether we're talking civilians or whether we're talking Gulf War veterans. We want to be well or at least we'd like to be better.

If you refer to the chart that's up there, it's just a chart that I've created over the years for discussion points with patients, with various government officials, whatever. It's a series of observations on the MCS phenomenon to sort of help better understand the disability. The first thing I'd say, and in a way it's reiterating a statement that was made by several of the panels, the Gulf Vet panels this morning, that is to look to the patient. Observe what is happening to the patient, again civilians/veterans. The patient experience in my mind very much holds the key to enlightening physicians and researchers with regard to the nature of the illness and disability, and what needs to be done. The first several comments on the sheet, symptoms come and go depending on exposure, reactions may be immediate or delayed, the same exposure may trigger different symptoms for different individuals but that sort of relationship remains the same, and predictable symptom patterns evolve over time and these patterns may vary from person to person.

Those who would deny the existence of MCS frequently argue that the symptoms are chaotic. MCS is not chaotic. For the most part, you see predictable patterns, and to my mind, very much the differences you see are variations on a theme. Just again, at an observational level, if you're looking to some degree at patients who've had pesticide exposures, you see significant central nervous system symptoms and more respiratory system involvement. The fifth item up there, the exposure response relationship, may be more difficult to tease out if the individual has multiple exposures or significant levels of exposure.

That's partly my experience over 6 years, that little modifications don't make any difference if you have big things that are background noise there. And it's very difficult to tease out those threads. I think this observation is critical, again, in understanding the nature of the disability and in sort of planning a research agenda. Again, just at my level of experience, two times during the first year that I was so very, very sick and disabled, we left the house, I was very sick, we left the house once going to my brother's, once going to a motel to see whether I would feel any better. I felt different, but no less sick, different symptoms, but no less sick. And, again, I had no context to measure what did this mean, what was this about?

The same thing, just one patient of the sort of thousands and thousand, a woman who had made major changes in her home, in her lifestyle, and as we discussed the various pieces of her life, it turned out that her husband worked in the particle board industry. He returned every day from work dressed in the clothes that he wore on the job, took them off at home, they were washed at home. When she made a change, that is that he no longer came home in that clothing, it was a remarkable difference for her.

Again, the nature of the disability, to my mind, also argues against using exposure or

environmental chambers. I just think that it's a bad practice to be in because we have that strong possibility of getting false positive and false negative results. I think that it doesn't have a lot of value in identifying MCS patients, for people who don't know they have chemical sensitivity I don't think there's a value there. And the other point is the fact that I think that it diverts our attention for the critical need for an environmental medical unit on the order of what Bill Meggs spoke about earlier so that we can take patients, de-adapt them, re-expose them, find out if indeed people are sick from low level exposures.

Another point I think that needs to be made is that we really need team approaches to looking at patients, again whether they're civilians or veterans. One model that I see in the Occupational Health Clinic in New York State is that the team has an occupational health doctor, a nurse, case worker, educator, social worker, and industrial hygienist. An although their patient population is 250 people, 10 percent of their entire patient population, nevertheless, the investment of time and energy is much more substantial. And ultimately the VA and other health organizations are going to have to invest that time and money if they're going to help people who are sick in this fashion.

The final point that I want to make very briefly is over the controversy of the diagnosis of MCS, and again to refer back to Bill Meggs, the perhaps manufactured controversy. But if we go back a few years in the civilian MCS population, there was a period where I spoke with many patients who clearly knew that their predominant symptoms were hypersensitivity to chemicals, but they chose to describe themselves as CFS patients, as chronic fatigue patients, because they thought that it was more socially acceptable. I'd suggest to Gulf War veterans who are sick that they need to get past that controversy issue which might make them shy away from avoidance, which I think would be a critical piece in identifying their problems and their intolerances. Thank you. Thanks for that extra second.

Dr. Claudia Miller, Moderator

Our next speaker is Dr. William Rea. Dr. Rea is a practicing thoracic and cardiovascular surgeon, but better known to most of us for his work on environmental aspects of health and diseases, perhaps one of the messengers in this area and has seen, I don't know, last count was tens of thousands of patients, but I don't remember now. He is the founder of the Environmental Health Center in Dallas, and he's currently director of this highly specialized medical facility. Dr. Rea.

William Rea, MD, FACS
Director, Environmental Health Center
Dallas, Texas

Thirty thousand patients. Thank you, Claudia. Now that you've given my talk, I'll just be quiet. I would like to say a few observations that I've learned over the last 25 years of taking care of chemically sensitive patients. And we've had a lot of beautiful research and talks here today, but I

want to caution people as a vascular surgeon, I see many patients who have no brain dysfunction, no measurable brain dysfunction. Professor Butler and I, at the University of North Texas in a controlled environment in a hospital wing, did numerous studies and we found subsets of patients who did not have the brain dysfunction. So I think today we're talking about a subset. It may be a predominant subset, but it depends on your point of view. If you consider that, then you don't have so much problem with all this psychological nonsense, because I've not seen blood vessels rupture on the skin due to psychological dysfunction, and I've never seen any reported in the literature. Yes, you do have vascular spasms, and as Dr. Simpson pointed out from New Zealand, there is certainly oxidative degeneration of both the homeostasis and the erythrocytes and lymphocytes that's well known now in physiology which could explain a lot.

So, I think we should realize there are many mechanisms for the chemical sensitivity and that, in our opinion, there's not usually one trigger unless you're in a large explosion. One thing we have seen, talking about this subset of patients who have the brain dysfunction group, and also the other groups so far as that goes, you may have an initiating agent which is gone, and then there are propagating agents that keep the people ill over and over. I was hoping to hear that earlier today when the people talked about the neurological, some of Dr. Spencer's stuff, and some of the others. Because in our experience, you don't have to have the continuation of the same agent. But what appears to happen, from the clinical things that we've seen, that for example you may get hit with organophosphate pesticides and then a brother comes along and it starts propagating it, and then a sister and then a cousin, and then before you know it, unrelated chemicals, and then eventually even foods will trigger this in those that are super, super sensitive. So, you want to keep that in mind when you're trying to diagnose and treat these patients.

Now, we have, I thought I would show you, we've done over a thousand triple camera SPECT scans by the method of Simon and Hickey. And I heard earlier today, I believe it was from Dr. White from Boston, that scans aren't very good and don't show a similar pattern. That's not been our experience. We searched the University of North Texas which has 25,000 students and we did find 25 we thought had normal brains, and did SPECT scans on them, and sure enough they met all the criteria for cleanness. They had smooth areas, they had equal flow and function, and so on.

But here's a Gulf War veteran who has had 3 SPECT scans over the years and has showed a distinct improvement in the scan as he got treated. On your right is the first scan showing flow and function, and as you will see on this patient in the flow area, he had lots of areas of the green color there which should be all yellow. And therefore, he'd had decrease in flow, and he'd had a little bit of frontal lobe dysfunction. He had what we call hot and cold areas. The function part of the triple camera SPECT is glutathione dependent, and if you do use a single or double camera one, you won't see these changes on a consistent basis in the chemically sensitive individual.

This is in '93 after we'd just started treating him for a few months. He did start getting better.

He's had some less scan. But in '95 you can see his flow was totally restored. This patient had severe disequilibrium when we initially saw him. He was an auto mechanic right back of the front lines, and he told me about 18 hours a day he was breathing the exhaust of the trucks and he knew it was getting him.

So, I think that this is an area, if you're going to do the subset of brain dysfunctions, if you use Simon and Hickey's method, you will get reproducible data. As I say, we've done over a thousand of these on the chemically sensitive and it has held very true.

Now, the other point I'd like to make, I believe it was Dr. Clauw at Johns Hopkins that suggested that the autonomic dysfunction is very predominant in these patients. We've seen that. We've measured about 2500 chemically sensitive patients with objective autonomic function tests from Professor Ishikawa at the Kyoto University in Japan. We've seen 93 percent of the people have autonomic dysfunction across the board. So, I think he's right-on on that.

Well, let's go to treatment a little bit. We keep talking about avoidance, but you know getting well, and people with chemical sensitivity do get well, and a lot of them get well. In fact, in our long-term follow-up on the worst cases we had to put in the hospital, 80 percent of them got better and returned to their jobs. Okay? So, it's not out of the realm. It's not something magic, and you can help them. But you do have to decrease the total body load of pollutants in air, food and water. You need to give nutrition supplementation. You've got to treat the secondary allergic sensitivities. I believe Bill Meggs said before, we use heat therapy and a form of dry saunas to mobilize the toxics better. And sometimes when you get them cleaned out, and you can monitor their blood levels for toxics, you will find that they've got a damaged homeostatic mechanism, and that you may need immune modulators like transfer factor or autogenous lymphocytic factor.

In closing, I want to say that in the long-run, medication treatment appears to give adverse effects to these patients. You might want to use it a little bit for some acute situation for a week or two or a month, but long-term treatment you get exacerbation of the chemical sensitivity in our experience. Thank you very much.

Dr. Claudia Miller, Moderator

Thank you. Our next speaker is Ms. Cynthia Wilson. She is the founder and executive director of the Chemical Injury Information Network headquartered in White Sulfur Springs, Montana. Ms. Wilson is also the Editor in Chief of ***Our Toxic Times*** and has written a few books on this subject. She herself became ill and perhaps will tell us about that experience and about the experiences of the people that are part of her advocacy group. Ms. Wilson.

Cynthia Wilson

Executive Director and Chairmen of the Board
Chemical Injury Information Network and Environmental Access Research Network
White Sulphur Springs, Montana

I run the Chemical Injury Information Network and currently right now, we appear to be the largest support group dealing with multiple chemical sensitivities in the world, so we have a huge database of victims that we deal with.

But, in recent months, or recent weeks, I found an article written by Jackson Parkhurst who quoted an old adage that pointed to the fact that when there's no cure for something, there'll be a multitude of treatments for it. And that is the case in multiple chemical sensitivity. Several surveys over the last couple of years have documented over 100 different MCS treatments being offered at any given time. While the surveys show that most of the treatments provide some degree of relief, they also show that no treatment has been curative. The treatments fall roughly into 4 categories that have nothing to do with the efficacy of the treatment being offered. It's not my intent here to do value judgements on different treatments, but only to show how the Chemical Injury Information Network separates them out and views them.

The first treatment category is what CIIN refers to as the "no harm, no foul" treatment. Again, efficacy is not an issue here. This category is defined by whether the treatment has the potential to make the patient worse. There are a lot of treatments being offered that do have that potential.

The second category makes up that. It is the treatments that have a significant downside. With these treatments, not only is the patient unlikely to recover, but the patient risks being made worse. For this reason, CIIN, the group I run, opposes several very popular MCS treatment programs because it feels that the risk versus the benefits are simply not being disclosed to the patients.

The third category of treatment is legitimate and necessary, but doesn't directly affect the MCS. It involves treating those illnesses and conditions that run concurrent with MCS. As one doctor put it, "You have to treat the problems that are treatable." Conditions like allergies, asthma are frequently found in people with MCS. And while having MCS may complicate the situation, these concurrent conditions should not go unattended.

The fourth category of treatment is one that is universally accepted as being beneficial and just as universally hated by MCS sufferers, and that's avoidance. Avoiding those things that make you sick. Avoidance is simple in concept but not very easy in execution. It wreaks havoc on families as spouses and children become resentful that MCS sufferers' conditions interfere with their ability to live normal lives. And tracking down chemical triggers can be a long painful process of trial and error that most sufferers would just rather avoid.

Most psychologists estimate that it takes an average of 3 years to complete the learning curve to successfully manage the illness. Yet, MCS doesn't have to be a slow progression into declining health. Avoidance builds tolerance. It takes time, but it works. Tolerance leads to MCS sufferers feeling almost normal. Sufferers begin to feel so good that many mistake it for being cured. One MCS sufferer actually wrote a book about how she cured herself and her daughter. During a radio interview to promote her book, the woman admitted that neither she nor her daughter could tolerate such things as perfumes, detergents, pesticides, or vehicle exhaust without getting sick. That's not a cure. But this woman isn't alone in trying to treat tolerance as a cure. At least twice a month someone will call to say that they've cured themselves and want to share how they did it with other CIIN members. On questioning, not a single individual claiming to be cured can tolerate a normal environment.

I can sympathize with mistaking feeling better for a cure. When I started feeling better, I had to fight the urge to reenter my old life, but I knew from too many phone calls from other CIIN members and from a couple of unexpected exposures, that I was nowhere near being cured. In fact, I was on very dangerous ground. CIIN has literally had hundreds of phone calls from MCS sufferers who believed they were getting cured, and when that belief was shattered, these people were devastated. They all felt so well that they had decided to visit a friend in the hospital, go to a wedding, or simply take part in some other normal activity without accommodating their MCS. And then they got an exposure that undid years of avoidance, and in most cases left them feeling worse than they had before. Universally they felt that they were almost cured. One woman even called herself 98 percent cured, and the setback devastated her. And now they fear that they're never going to regain that health again.

These are just some of the experiences that have led CIIN to hold treatments to an extremely high standard for this illness. Another reason that we hold it to such a high standard is that the organization believes that before an effective treatment for MCS, or even a cure can be found, someone first has to discover what it really is. Until then, MCS treatments will be a dime a dozen and anyone with a good bedside manner has a license to steal from people who can ill afford it.

Dr. Claudia Miller, Moderator

Our last speaker will be substituting on the panel for Dr. Grace Ziem who was unable to be attending today. Albert Donnay is a research associate of hers and director of MCS Resources and Referral. He asked to have just about 4 minutes to present a couple of the slides that she would have done had she been here.

Mr. Albert Donnay

Thank you. Dr. Ziem also asked me to tell you why she is not here. She decided to boycott this meeting in protest when she learned that the Department of Defense, without waiting for the

research recommendations of this conference, which admittedly are directed at civilian agencies, issued $67 million dollars in research solicitations for research in the areas we're talking about, including $3 million for research into MCS, chronic fatigue syndrome, and fibromyalgia combined. We're glad to see that, but we wish they'd waited for our recommendations.

In 1996, exactly 3 years ago to the day, this data was presented by Dr. Ziem and I to the Presidential Committee on Gulf War Illnesses. We showed that CFS, FMS, and MCS have all the same symptoms in the literature. We checked 200 references of each of these diseases, and here are the top 10 symptoms of Gulf War illness according to the DoD CCEP. We showed at the bottom that we could also find 3 things the DoD was not tracking:

- Symptoms wax and wane in response to various stressors, and that's reported in all 3 of these diseases;

- Photosensitivity to sunlight is a problem in all 3 of these civilian diseases; and

- There's a chemical sensitivity to drugs and other ingested chemicals.

These were not tracked, and we asked why it was that VA and DoD were not tracking these, and of course, we encouraged them to do that.

We then looked at the literature to see what we could learn about this overlap and found that very little had been studied about the overlap. While there's a lot of literature on each of these diseases, this is a look of just the last decade, I believe the total n is over 2000 here. You see big chunks of literature on fibromyalgia, MCS, and CFS, but very little on the overlap. There are just 4 papers looking at this overlap with fibromyalgia and MCS, 13 with CFS, and a bit more with the overlap of fibromyalgia and CFS. In the middle there's a 3, that's 3 papers in the last decade that looked at the 3-way overlap of all 3 diseases.

So, we set out to look at her patients and did a study of 100 new patients as they came to her specialty practice and classified them as male, female, or combined according to which of these diseases they had. Here is only MCS over here, people who did not have any chronic fatigue syndrom criteria or fibromyalgia criteria using 1990 American College of Rheumatology criteria for fibromyalgia including the pressure point exam, or tender point, and using the CFS 1994. 10 percent, no difference really between men and women. Amazingly almost no one, just 2 women, had multiple chemical sensitivity with fibromyalgia and no chronic fatigue. This is telling us something important. Here's where everybody was. If you look at the white combined male and female, here is MCS with chronic fatigue syndrome, and the last one is all three. What's fascinating to me there is that the largest single group of combined was 47 percent with all 3, the next largest group was 41 percent with the CFS. If you don't break out the male and female, you think that's the same group. But male/female shows an incredible new finding we believe that

deserves more research. The females, 2/3rds of the total out of a 100 were women. But when you just look at the female group, which is this one, almost 2/3rds of the women have all 3, but only 1/3rd of them have just CFS and MCS. The situation is exactly the opposite in the men. 2/3rds of the men have MCS and CFS, but only 1/3rd had all 3. The sex difference, the gender difference, is from fibromyalgia. There was not gender difference in the CFS or the MCS. In fact, as a percentage, slightly more men had CFS than the women.

So, our conclusion from this, and certainly it has implications for both clinical work and research, is that in any study, or any examination, any assessment of patients, of any of these 3 disorders, and especially Gulf War syndrome where we recognize all of them already, you need to screen for all 3.

In the Johns Hopkins study that we're both involved in of MCS immunology, we're selecting MCS patients, but we're also screening them for their fibromyalgia and their chronic fatigue status so when we'll know when we're done what we were really studying. We think these groups probably are very different. Certainly, the people who have all 3 are a lot sicker than the people who only have 1 or 2.

Just off the subject, but because Dr. Ziem asked me to mention it, with regard to treatment and assessment, she urges you to look for vitamin and mineral deficiencies. You will find them, and they're treatable and correctable, and it's very important to correct them. You also find low plasma levels and you can fix that with a recommendation for lots of water intake, more than a gallon a day is what she recommends. And finally to be aware that there are people with chemical sensitivity who have no sense of smell whatsoever. These anosmic people, however, still report entering environments where there may be chemical exposure and developing all the same pattern of symptoms. So, clearly this is not an odor induced mechanism, and one concern I have about Dr. Bell's otherwise very robust Chemical Odor Intolerance Index is that it is looking at chemical odors, and there are chemicals without odor, carbon monoxide is a good example, that produce the symptoms.

The closing point is, we beg to come out of this with a clinical definition of MCS because as a clinician she's repeatedly frustrated by having to defend her diagnosis without a clinical definition to point to, and without an ICD-9 code with which to code the disease. So, those are urgent priorities for ongoing clinical care of veterans and civilians. Thank you.

Dr. Claudia Miller, Moderator

I don't see people rushing to the microphone as before, and I really would appreciate it if we could forgo questions because we have mostly a clinical panel and we'd like to stay as close to the schedule of 4:00 meetings as we can. I want to give everybody ample time. I would close with one question and I'd ask so we'd know, who in the audience is a Gulf War veteran and who is ill?

I'd appreciate it if they would stand. Any ill Gulf War veterans in the audience, please stand. All right. Please stand. Some of you may not be able to. Keep standing. Okay, now, if you have any chemical intolerances, food intolerances, alcohol intolerance, or things that we've described here before, remain standing. Anyone else sit down. Okay. No one has sat down. This is obviously a very small sample, but it's certainly an experience I think a lot of us have shared. I appreciate your help and I'm going to ask Drue if she wants to help with breaking people into the groups for discussion.

Dr. Drue Barrett

The people in the audience are free to go to any of the workgroups that they want to go to. The Workgroup I, Pathophysiology will be in this part. We're going to split up this room. I believe Workgroup, I don't have the sheet in front of me, it's in your folder. Prevention will be in this room. The treatment and the assessment and diagnosis are in the rooms that are out this way. Assessment and diagnosis is in the Lombard Room, treatment is in the Gable Room, which are right out here. Prevention over here, pathophysiology over here.

The session adjourned

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